EXHIBIT 1

IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF TENNESSEE
WESTERN DIVISION

FREDDIE JONES, LUKE JONES, TRENNA JONES, RALPH JONES, LAVON JONES, and JIMMY FREEMAN, as Surviving Children of ELNORA JONES, Deceased, Plaintiffs, vs. ABBOTT LABORATORIES, Defendant.	Case No. 2:07-cv-02120-BBD-tmp JURY DEMAND

ABBOTT LABORATORIES' REPLY MEMORANDUM IN SUPPORT OF ITS MOTION FOR A PROTECTIVE ORDER QUASHING PLAINTIFFS' REQUEST FOR ABBOTT'S ADVERSE EVENT REPORTS DATABASE

Defendant Abbott Laboratories ("Abbott"), by and through its undersigned counsel, respectfully submits its Reply Memorandum in Support of Its Motion for a Protective Order Quashing Plaintiffs' Request for Abbott's Adverse Event Reports Database, and in support states as follows:

I. Plaintiffs Have Failed To Demonstrate A Particularized Need For The Production Of Abbott's AEGIS Database Because Their Proposed PRR Analysis Is Irrelevant.

Plaintiffs do not dispute that because Abbott has already produced the adverse event reports for Humira involving cancers in electronically text-searchable PDF format, the Rules of this Court require them to "demonstrate a particularized need" for production of that same information in its native format. L.R. 26.1(e)(6); *see also* Dkt. # 150 at 8-10. The sole "particularized need" that Plaintiffs identified at the June 13, 2011 hearing was that the database

is necessary to conduct proportional reporting rate ("PRR") analyses of Humira adverse event reports. As described by Plaintiffs, they plan to use PRR analyses to compare the reporting ratios of one adverse event coincident with the use of Humira to another—e.g., lymphomas and infections. Plaintiffs, however, misunderstand the function and purpose of PRR analyses. PRR analysis is not intended to compare reporting ratios of different adverse events associated with the same drug. Instead, it compares the frequency of spontaneous reports of a specific adverse event for a particular drug with the frequency of reports of that same adverse event for ***other*** drugs.[1] Moreover, Plaintiffs have presented to the Court no case law, FDA guidance, or any other authority whatsoever (and Abbott has found none) to support Plaintiffs' argument that their "version" of PRR analysis is an accepted means of signal detection in pharmacovigilance planning.

Even if Plaintiffs intend to conduct a traditional PRR analysis and compare the reporting ratio of cancers for Humira with the reporting ratio of cancers for other drugs, the calculations produced by such analysis would be irrelevant to any claim or defense in this case—particularly Plaintiffs' causation inquiry. The FDA has specifically determined that "data mining techniques" such as PRR analysis are "not a tool for establishing causal attributions between products and adverse events." FDA Final Guidance, "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment" (March 2005), Sec. IV.E, at *7 (attached hereto as Ex. C). The FDA has also acknowledged that techniques like PRR analysis "are still in development and their usefulness for identifying safety signals is being evaluated[,]" that they "do[] not quantify the magnitude of risk, and [that] caution should be exercised when comparing drugs." FDA

[1] *See generally* S. J. W. Evans, et al., "Proportional Reporting Ratios: the Uses of Epidemiological Methods for Signal Generation [abstract]," Pharmacoepidemiology and Drug Safety 7:S79-S215 (1998) (attached hereto as Ex. A); S. J. W. Evans, et al., "Use of Proportional Reporting Ratios (PRRs) for Signal Generation From Spontaneous Adverse Drug Reaction Reports," Pharmacoepidemiology and Drug Safety 10:483-486 (2001) (attached hereto as Ex. B).

Final Guidance, "E2E Pharmacovigilance Planning" (April 2005), Sec. IV.1, at *8 (attached hereto as Ex. D).[2]

There is no dispute in the pharmacovigilance literature that PRR analysis is not a means of demonstrating causation; instead, it is simply one technique for a drug manufacturer "to detect potential signals for further evaluation." *See id.* Moreover, several commentators have criticized the use of PRR analysis even for this extremely limited purpose, because the analysis is based entirely on adverse event reports—widely recognized as an incomplete and biased data source. *See, e.g.*, Brian L. Strom, "Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions: A Counterpoint," JAMA, Vol. 292, No. 21, Dec. 2004, at 2644 (criticizing analyses like PRR as "formal statistical analyses of poor, incomplete, and biased data" and noting that "[n]o matter how sophisticated, analyses of such data can readily be misleading.") (attached hereto as Ex. E).

And as this Court has already noted, all other courts that have addressed the issue have specifically rejected use of PRR analyses in product liability litigation, finding that it "does not speak to the issue of causation" and that "proportional reporting rate analyses are incomplete and often misleading[.]" *In re Meridia Prods. Liab. Litig.*, 328 F. Supp. 2d 791, 807 (N.D. Ohio 2004); *see also id.* at 808 (finding that "this determination is consistent with other courts' conclusions regarding proportional reporting rate analyses" and collecting cases). Plaintiffs' Response fails to address *In re Meridia* and does not explain how their proposed PRR analysis would be any more relevant in this case. Because the results of any PRR analysis sought by Plaintiffs would be of questionable relevance at best, the enormous burden of producing the database outweighs Plaintiffs' purported "particularized need" for the data.

---

[2] *See also id.* ("Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate among different drugs and the many potential biases inherent in spontaneous reporting.").

II. Even If Plaintiffs' Proposed PRR Analysis Were Relevant, Plaintiffs Have Not Shown That They Need Data From Abbott's AEGIS Database To Conduct It.

Even if Plaintiffs' proposed PRR analysis had any relevance to their claims, Plaintiffs have not demonstrated why they need Abbott's entire AEGIS database to conduct their analysis. First, in order to compare the reporting ratios of Humira to other drugs, Plaintiffs require access to the AERs of these other drugs, which are not contained in Abbott's database. Presumably, Plaintiffs' experts will obtain this data from the FDA's Adverse Event Reporting System ("AERS"), which collects adverse events reports for all drugs from all manufacturers and other sources. Because the FDA database contains the AERs for Humira and all other drugs, Plaintiffs simply have no "particularized need" for Abbott's AEGIS database. Second, the standard PRR equation requires only the cumulative number of adverse event reports of interest (here, cancers) and the total number of all adverse event reports, and does not require the number of other adverse event reports (for example, infections or neurological disorders) or any other information from the AEGIS database (for example, narrative fields).[3] In short, the production of the entire AEGIS database is not required for Plaintiffs to conduct a PRR analysis. Plaintiffs have made no argument and provided this Court with no reason why Abbott should undertake the burden and expense of producing its database in native format, given that PRR analysis—Plaintiffs' ***only*** claimed reason for why they need the database—can be performed by using other readily accessible data.

---

[3] The standard PRR equation is $a/(a + b)$ divided by $c/(c + d)$, with the variables defined as follows:

	Reaction(s) of interest	All other reactions
Drug of interest	*A*	*b*
All other drugs in the database	*C*	*d*

See, e.g., Nicholas Moore, et al., "Biases Affecting the Proportional Reporting Ratio (PRR) in Spontaneous Reports Pharmacovigilance Databases: the Example of Sertindole," Pharmacoepidemiology and Drug Safety 12:271-281 (2003), at 272 (attached hereto as Ex. F).

III. Plaintiffs Ignore The Authorities Cited By Abbott And Rely Exclusively On Unreported Orders That Have Little To No Persuasive Force.

Plaintiffs do not even attempt to rebut the many authorities Abbott cited in its opening brief that establish that Plaintiffs are not entitled to the database on the grounds of irrelevance, cumulativeness, and burden. (*See* Dkt. # 150.) Instead, Plaintiffs rely exclusively on two ***unreported*** orders from foreign jurisdictions—orders that include virtually no analysis of any of the issues raised in Abbott's brief and, between the two of them, cite to just one published decision. These orders have little to no persuasive force.

In addition, the orders cited by Plaintiffs are not apposite here. Plaintiffs in *In re Neurontin* argued that the databases were relevant to their claim that defendants "market[ed] their drug Neurontin for . . . 'off-label' uses" for which they "had reason to know it was not safe." (*See* Resp., Dkt. #153, Ex. B, at 1.) The court agreed, finding that adverse event reports may be relevant to determine the extent of off-label use and defendants' awareness of it. (*See id.* at 2.) Here, however, Plaintiffs have asserted no such comparable need for Abbott's database.[4] And as Abbott has already explained, even the significant burden of producing a much smaller database in the Depakote litigation in *Rix v. Sanchez* cannot be compared to the burden of having to produce the entire Humira database—which contains over five times as many adverse event reports. (*See* Dkt. #150, at 7-8; 16-17). Unlike the *In re Meridia* court's careful articulation why a PRR analysis is irrelevant, the *Rix* court does not even discuss the issue or otherwise explain the relevance of the database. Discovery, while broad, is still closely tethered to concepts of relevance. *See* Fed. R. Civ. P. 26(b)(1); *Allen v. Howmedica Leibinger, GmhH*, 190 F.R.D. 518, 522 (W.D. Tenn. 1999) ("The party seeking discovery must be able to 'articulate the possible

[4] The *In re Neurontin* court also rejected the defendant's burden arguments because they were "conclusory." *See* Resp., Dkt. #153, Ex. B, at 3. Here, by contrast, Abbott has supported its burden arguments with a detailed declaration, which will be supplemented with live testimony at the June 23rd hearing.

linkage between the discovery sought and admissible evidence.'") (citation omitted). Moreover, neither of the orders cited by Plaintiffs address the situation here, where Abbott has already produced the AER data in the format requested by Plaintiffs' original counsel.

IV. Plaintiffs' Technical Expert Should Not Be Permitted To Participate In The June 23, 2011 Hearing Without Prior Disclosure of His Testimony.

Finally, Abbott objects to Plaintiffs' last-minute tendering of Keith Altman, Plaintiffs' "technical expert" (Resp., Dkt. #153 at 4), as a witness at the upcoming June 23, 2011 hearing without prior disclosure of his testimony. In support of its motion for a protective order, Abbott submitted a declaration from its employee Jody Trieloff that provides detailed factual support for its argument that the enormous burden of producing the AEGIS database outweighs the questionable relevance of the information. (Dkt. #150, Ex. B.) Rather than respond with their own declaration, Plaintiffs advised Abbott on June 21, 2011—***two days*** before the hearing—that they intend to present Mr. Altman as a witness. Since then, Plaintiffs have provided no information whatsoever as to Mr. Altman's qualifications, formal training, or experience, or what his proposed testimony will be. Plaintiffs' efforts to inject new issues into a fully-briefed motion at the eleventh hour should be denied, and they should not be permitted to tender Mr. Altman at the June 23, 2011 hearing.

CONCLUSION

For the foregoing reasons, Abbott respectfully requests that this Court grant its motion for a protective order and quash Plaintiffs' request for production of the AEGIS database for Humira.

Date: June 22, 2011

Respectfully submitted,

s/

Michael P. Foradas
Renee D. Smith
Andrew P. Bautista
Kirkland & Ellis, LLP
300 North LaSalle
Chicago, IL 60654
Telephone: 312.862.2000

Jill M. Steinberg (#11603)
Emily Turner Landry (#22157)
Robert F. Tom (#26636)
Baker, Donelson, Bearman,
Caldwell & Berkowitz, PC
165 Madison Avenue, Suite 2000
Memphis, Tennessee 38103
Telephone: 901.526.2000
jsteinberg@bakerdonelson.com
elandry@bakerdonelson.com
rtom@bakerdonelson.com

Attorneys for Defendant Abbott Laboratories

CERTIFICATE OF SERVICE

The undersigned hereby certifies that on this 22nd day of June, 2011, a copy of the foregoing was served on the parties listed below via operation of the electronic filing system of the United States District Court for the Western District of Tennessee:

Arnold Anderson Vickery
Fred H. Shepherd
One Riverway, Suite 1150
Houston, TX 77056

Edmund J. Schmidt III
Law Office of Eddie Schmidt
1720 West End Ave., Suite 300
Nashville, TN 37203

s/

EXHIBIT A

Pha

Pharmacoepidemiology AND DRUG SAFETY

VOLUME 7 SUPPLEMENT 2 AUGUST 1998

Official Journal of the International Society for Pharmacoepidemiology
and
The European Society of Pharmacovigilance

ABSTRACTS
14th International Conference on Pharmacoepidemiology
Berlin, Germany
16–19 August, 1998

Visit Wiley Journals Online
www.interscience.wiley.com

ISSN 1053–8569

WILEY
Publishers Since 1807

PDSAEA 7(S2) S79–S228 (1998)

VOLUME 7 SUPPLEMENT 2 AUGUST 1998

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY

ABSTRACTS

14th International Conference on Pharmacoepidemiology

Berlin, Germany

16–19 August, 1998

Announcement: Please note that in future abstract supplements, the Publisher will not require assignment of copyright in each abstract but will require a full permission to publish on the terms specified in the submissions form. The Publisher would like to apologise for any inconvenience caused during the production of this issue to those who have submitted abstracts.

Indexed or abstracted by 'Biosis', 'Cambridge Scientific Abstracts', 'Chemical Abstracts Service', 'Current Awareness in Biological Sciences', 'Current Contents/Clinical Medicine', 'Excerpta Medica—EMBASE', 'International Pharmaceutical Abstracts', 'Medical Documentation Service', 'Research Alert', 'Science Citation Index', 'SciSearch' and 'Statistical Theory & Method Abstracts (STMA)'

PDSAEA 7(S2) S79–S228 (1998) ISSN 1053–8569

$n = 131$). We compared Advil to Aleve, another propionic acid-derived OTC product. For the initial 22 months of Advil and Aleve marketing there were, respectively, 109 and 8222 total SAERs: 46 and 663 15-day Alerts; 12 and 127 serious; 51 and 7434 non-serious; approximately 6.3 billion and 3.4 billion doses distributed. The annual rate of 15-day Alerts and serious reports for Advil declined over the 13-year period; for the period May 1996 to March 1997, a total of 10 were received, constituting less than 5% of reports received ($n = 209$).
Conclusion — Most Advil SAERs were non-serious, transient events; the SAER rate is extremely low relative to over 59 billion doses distributed. Comparison of SAER data with another propionic acid analgesic over different time periods supports the favorable safety profile of Advil.

055. Proportional Reporting Ratios: The Uses of Epidemiological Methods for Signal Generation

S. J. W. Evans, P. Waller and S. Davis. *Post-Licensing Division, Medicines Control Agency, 1 Nine Elms Lane, London SW8 5NQ, UK.*

KEY WORDS — signal-generation; epidemiology; spontaneous reporting

Background — 'Proportional Reporting Ratios', which are analogous to proportional mortality ratios, have been used as an epidemiological approach to analysis of spontaneous reports of suspected adverse drug reactions (ADRs) where the true number of patients exposed to a drug is unknown.
Methods — The proportion of suspected ADRs on the UK ADROIT database with a particular reaction, classified by 'Preferred term', for a particular drug is compared with the proportion for that term for all drugs — a Proportional Reporting Ratio (PRR). Statistical significance tests of these ratios should not be over-interpreted, but a plot of PRR against chi^2 is helpful, with criteria of PRR > 2 and $chi^2 > 4$ with > two cases suggesting a signal.
Results — Examining historical data about 60% of signals identified by this method were known and in marketing authorizations and product information. Assessment of those new signals which have led to reviews shows that about 50% have led to requests for changes in marketing authorizations and product information. Changes in PRR over time add to both the sensitivity and specificity of the method for signal generation.
Discussion — Spontaneous reporting has well known advantages and disadvantages; this method aids the interpretation of such data. The MCA now makes routine use of the method to compare proportions of suspected ADRs between different drugs or groups of drugs, for signal generation or preliminary evaluation.

056. What is the Drugs Bill for Diabetes? A Population-based Study

J. M. M. Evans[1], D. I. R. Boyle[1], P. G. Davey[1], R. W. Newton[2], T. M. MacDonald[1], R. T. Jung[2] and A. D. Morris[1,2,3] for the DARTS/MEMO Collaboration. [1]*Medicines Monitoring Unit (MEMO), University of Dundee, UK;* [2]*Diabetes Centre, Ninewells Hospital, Dundee, UK;* [3]*Department of Medicine, University of Dundee, UK.*

KEY WORDS — diabetes; cost; drug utilization; pharmacoeconomics; record linkage

Introduction — There are few data on direct costs of drug treatments in diabetes, although it is suggested that utilization of even non-diabetic preparations is higher for diabetic patients.
Methods — The DARTS/MEMO Collaboration investigated drug usage of diabetic patients identified from the DARTS register (prevalence 1.94%; sensitivity 97%; PPV 97%) over 2 years (1993–1994). A total of 777 IDDM and 6310 NIDDM patients were compared with 1554 and 12,552 population-based comparators respectively, matched for age, sex and GP practice. The excess costs of non-diabetic drugs were calculated.
Results — Excluding antidiabetic preparations, an average of 21.7 prescription items per IDDM patient were dispensed (total 16,879), compared with 10.2 per comparator. Prescribing was higher among IDDM patients for every drug category, with the biggest differences for cardiovascular drugs (×3), and CNS drugs (×2). Average cost per item was £10.58 and the estimated overall cost was £178,593 or £115 per IDDM patient per year, compared with £52 per year for each comparator. There was a 1.5-fold increase in prescribing in NIDDM patients compared with comparators (e.g. cardiovascular drugs ×2; CNS drugs ×1.5). An average of 48.5 prescription items were dispensed to each NIDDM patient (total 306,272), compared with 31.3 per comparator. Estimated costs were £248 per NIDDM patient per year, compared with £153 per comparator per year.
Conclusion — The increased usage evident within every drug category by diabetic patients has significant cost implications.

EXHIBIT B

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2001; **10**: 483–486
DOI: 10.1002/pds.677

ORIGINAL REPORT

Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports

S. J. W. Evans, P. C. Waller* and S. Davis

Post-Licensing Division, Medicines Control Agency, Market Towers, 1, Nine Elms Lane, London SW8 5NQ

SUMMARY

Background The process of generating 'signals' of possible unrecognized hazards from spontaneous adverse drug reaction reporting data has been likened to looking for a needle in a haystack. However, statistical approaches to the data have been underutilised.

Methods Using the UK Yellow Card database, we have developed and evaluated a statistical aid to signal generation called a Proportional Reporting Ratio (PRR). The proportion of all reactions to a drug which are for a particular medical condition of interest is compared to the same proportion for all drugs in the database, in a 2×2 table. We investigated a group of newly-marketed drugs using as minimum criteria for a signal, 3 or more cases, PRR at least 2, chi-squared of at least 4.

Findings The database was used to examine retrospectively 15 drugs newly-marketed in the UK, with the highest levels of ADR reporting. The method identified 481 signals meeting the minimum criteria during the period 1996–8. Further evaluation of these showed that 70% were known adverse reactions, 13% were events which were likely to be related to the underlying disease and 17% were signals requiring further evaluation.

Implications Proportional reporting ratios are a valuable aid to signal generation from spontaneous reporting data which are easy to calculate and interpret, and various refinements are possible.

KEY WORDS — drug safety; pharmacovigilance; signal generation; spontaneous AD reporting

INTRODUCTION

The primary purpose of spontaneous adverse drug reaction (ADR) reporting is to provide early warnings of hazards which have not been recognized prior to marketing of a drug because of limitations of clinical trials in respect of sample size, duration and generalisability to ordinary practice. The process of scrutinising spontaneous ADR data for hazards is known as signal generation. Once a signal has been generated, other sources of data are investigated and, if there is sufficient evidence of a public health issue, steps are taken by regulatory authorities aimed at minimising the risks and informing users.[1]

In the UK, reports of suspected ADRs are made on Yellow Cards by health professionals and are sent to the Medicines Control Agency (MCA) where they are entered onto the Adverse Drug Reactions On-line Information Tracking (ADROIT) database.[2] This database, which came into operation in 1991, contains more than 350 000 reports received from the beginning of the Yellow Card scheme in 1964, describing about 600 000 reactions.

If an adverse reaction is a rare disease then a signal may be generated by a small series of around 3–5 reports. However, in general, there is no easy answer to the question 'How many reports constitute a signal?'[3] This involves judgements being made based on the number and quality of the case reports, the nature of the adverse reaction, type of drug and level

* Correspondence to: Dr P. C. Waller, Post-Licensing Division, Medicines Control Agency, Market Towers, 1, Nine Elms Lane, London SW8 5NQ. Fax: 0207-273-0205.

Received 2 November 2001
Revised 7 November 2001
Accepted 9 November 2001
Published online: 10 December 2001

of usage. There is a need to develop tools to aid and improve this process, and in particular to ensure that recognition of important signals is not delayed because the needle cannot be seen in the haystack.[4]

In this paper we describe a statistical aid to signal generation, the value of which we have explored in the ADROIT database.

METHODS

In order to judge whether the number of cases reported spontaneously exceeds what might be expected through a combination of chance and background 'noise', there are two accepted approaches.[5] The first involves using denominator data related to use of the drug (often dispensed prescriptions or sales as a proxy) and calculating reporting rates (reporting rate = no. of reports/no. of prescriptions). Comparisons between drugs based on reporting rates may be biased by many factors such as increased reporting for new drugs, and the effects of calendar time and publicity. Little weight can be placed on small differences in reporting rates between drugs but large differences (i.e. several-fold) may represent a signal worthy of investigation. The second approach is to use the total number of reports for the drug as a denominator and to calculate the proportion of all reactions which are the type of interest (e.g. hepatitis). This proportion may be compared with the value for other drugs and it is also possible to compare complete profiles of ADR reporting for drugs, where differences in the profile may represent signals. This proportionate approach has some advantages over reporting rates. First, no external data are needed and the limitations of such data (including delay in receipt) do not apply. Secondly, it may be expected to counteract some of the biases related to variable reporting. For example, if the overall level of reporting is high because of new drug bias, this will not necessarily affect the proportion of all reactions for the drug which are of a specified type.

We have developed a statistical aid to signal generation based on the proportionate approach which also utilises the stability of a large database. This involves calculation of the proportions of specified reactions or groups of reactions for drugs of interest where the comparator is all other drugs in the database. The result of such a calculation is called a proportional reporting ratio (PRR) where the PRR is $a/(a+c)$ divided by $b/(b+d)$ in a two by two table (see Table 1).

An example of such a calculation is given in Table 2. The expected or null value for a PRR is one and the values generated are measures related to strength of association which behave in a similar fashion to relative risks (the higher the PRR, the greater the strength of the signal). It is also possible to measure the size of the association using an odds ratio. Measures of statistical association may be calculated using a chi-squared test on one degree of freedom with Yates's correction. Judgement about whether or not there is a signal, and its strength, is made on the basis of three pieces of information i.e. the PRR, value of chi-squared and the absolute number of reports. An equivalent alternative to chi-squared is to calculate a confidence interval around the PRR.

Table 1. Calculation of PRRs

	Drug of interest	All other drugs in database
Reaction(s) of interest	a	b
All other reactions	c	d

Table 2. Example of a PRR calculation-rifabutin and uveitis

	Rifabutin	All other drugs
Uveitis	41	754
All other ADRs	14	591 958
TOTAL	55	592 712

PRR = 41/55 divided by 754/592, 712 = 586.
Chi-squared (1 df) = 22 740.

We tested the criteria using accumulated data for 15 newly-marketed drugs with the highest levels of ADR reporting during the period 1996–8. We examined whether the method would identify known hazards and possible adverse reactions which had not been previously recognized. A signal was defined as a PRR of at least 2, chi-squared of at least 4 and three or more cases. Using the ADROIT medical dictionary,[6] we calculated the PRRs for all reported preferred terms and asked the assessor responsible for monitoring the drug to evaluate all the signals meeting the above criteria to decide whether the ADR was recognized (on the basis of authorised product information), likely to be related to the underlying disease or a new signal worthy of investigation.

All calculations were performed using a standard statistical software program (STATA, Stata Corp, College Station, Texas).

RESULTS

In total, the method identified 487 potential signals meeting the minimum criteria (i.e. 10% of reported

Table 3. Evaluation of potential signals meeting minimum criteria for 15 newly-marketed drugs during the period 1996–8

Rank	Drug substance	Number of preferred terms reported	Number of potential signals* (% of number of PTs reported)	R	E	S
1	Venlafaxine	532	64 (12%)	52	10	2
2	Tramadol	390	38 (10%)	25	0	13
3	Lamotrigine	505	47 (10%)	24	8	15
4	Losartan	290	26 (9%)	14	4	8
5	Nefazodone	356	50 (14%)	37	7	6
6	Meloxicam	317	41 (13%)	41	0	0
7	Alendronic acid	300	37 (12%)	32	2	3
8	Dexfenfluramine	250	31 (12%)	20	0	11
9	Moclobemide	269	26 (11%)	7	15	4
10	Atorvastatin	264	28 (11%)	27	0	1
11	Citalopram	278	24 (9%)	16	1	7
12	Olanzapine	306	46 (15%)	27	10	9
13	Montelukast	255	15 (6%)	10	4	1
14	Mirtazapine	258	6 (2%)	6	0	0
15	Nicorandil	212	2 (1%)	1	1	0
Totals			481 (10%)	339 (70%)	62 (13%)	80 (17%)

The table excludes 6 unevaluable signals; *3 or more cases, PRR 2 or more, chi square 4 or more.
R = recognized adverse reaction, E = event considered to be related to underlying disease, S = signal requiring further evaluation.

preferred terms), of which 6 were excluded as unevaluable. The 15 drugs evaluated retrospectively, the total numbers of preferred terms reported for each drug, the numbers of signals identified and results of the evaluation are shown in Table 3. Of the 481 evaluable potential signals, 339 (70%) were recognized adverse reactions, 62 (13%) were considered to be events related to the underlying disease and 80 (17%) were signals requiring further evaluation. On average, the method identified about 5 unrecognised signals per drug (each of which had a high level of reporting). To date, of the 80 new signals identified, 22 (28%) have warranted detailed review, in 3 cases leading to a request for the manufacturer to change the product information. Of the remainder, 22 are being kept under review and no further action is proposed in relation to 36. The latter group includes 11 signals for dexfenfluramine, which was withdrawn from the market during the study period. The 339 recognized adverse reactions identified represented 71% of all the adverse reactions for these drugs listed in the 'undesirable effects' section of the Summary of Product Characteristics.

DISCUSSION

The mathematical basis of Proportional Reporting Ratios (PRRs) is straightforward and has been applied in other contexts where there are difficulties with denominators (e.g. proportional mortality ratios). A similar approach was developed by Finney in 1974[7], but has not been in general use subsequently.

Using data relating to recently marketed drugs, we found that PRRs within the ADROIT database for well-recognized ADRs were often strikingly high (e.g. more than 500 for uveitis associated with rifabutin, Table 2). Such problems are unlikely to be missed or even be detected much earlier using this approach. The main value is likely to be in highlighting a small series of cases where a PRR value of say 3–5 suggests a need for detailed evaluation of the series and further investigation. Conversely a PRR value close to or less than one may prevent unnecessary effort in evaluating case series which are the consequence of background 'noise' and do not truly represent a signal. The use of PRRs on a prospective basis is now performed routinely in the MCA.

Many potential signals are likely to be present in a large ADR database such as ADROIT. It is clear from our study that systematic use of PRRs identifies a high proportion of all recognised ADRs and also some new signals which might go unrecognised, at least until further cases are reported. The approach is not a substitute for detailed review of cases but an aid to deciding which series of cases most warrant further review. PRRs and chi-squared values are measures of association and not causality, and it is not surprising that some of signals identified were considered to be events unrelated to treatment.

When determining which possible signals to investigate further we consider four main factors: the strength of the signal, whether it really is new, the clinical importance (severity and seriousness) and the potential for preventive measures.[8] Those given the highest priority are Strong, New, Important and Potentially preventable (SNIP). The PRR represents a direct measure of the strength of the signal.

The main advantages of PRRs are that they are derived solely from spontaneous ADR data and are relatively simple to calculate and interpret. These factors are particularly important because of the dynamic nature of the data and consequent need for recalculation as potential signals emerge. As mentioned above, the proportionate approach may also help to avoid some of the biases caused by variable degrees of reporting.

One of the limitations of PRRs is that very striking signals for a particular drug will reduce the magnitude of the PRR for other signals with that drug. This is because large numbers of reports of a particular kind effectively inflate the denominator for that drug. Recalculation of PRRs excluding those reports is a possible approach to addressing this concern. A similar problem occurs when a class of drugs is associated with a strong signal as for non-steroidal anti-inflammatory drugs and gastrointestinal bleeding. Here these reports effectively inflate the numerator for all other drugs and reduce the value of PRRs for this ADR for all other drugs. In consequence drugs which do not produce GI bleeding tend to be associated with PRRs which are substantially less than one. Again, the problem could potentially be overcome by removing NSAIDs from the 'all other drugs' part of the equation.

There are a number of possible extensions to the method which need to be tested further and there is a need to evaluate the sensitivity and specificity of the method using varying minimum criteria. PRR calculations can be restricted to particular groups of drugs to fatal reports, or to particular time intervals. Examination of changes in PRRs over time may help to demonstrate how signals of adverse drug reactions can be identified as early as possible.

Our preliminary study has shown that calculation of proportional reporting ratios is a valuable aid to signal generation from spontaneous ADR data. Further research is needed to develop the method as a tool for routine pharmacovigilance.

CONTRIBUTORS

SE conceived the method and developed its application with PW. SD undertook the analyses described. PW wrote the paper with contributions and review from the other authors.

ACKNOWLEDGEMENTS

We acknowledge the guidance given by the late Dr. Susan Wood and would like to thank many colleagues at the MCA and on the Committee on Safety of Medicines and its Sub-Committee on Pharmacovigilance, who have contributed to this work.

REFERENCES

1. Waller PC, Coulson RA, Wood SM. Regulatory pharmacovigilance in the United Kingdom: current principles and practice. *Pharmacoepidemiol and Drug Safe* 1996; **5**: 363–375.
2. Wood SM, Coulson RA. Adverse Drug Reactions On-line Information Tracking (ADROIT). *Pharmaceutical Medicine* 1993; **7**: 203–213.
3. Begaud B, Moride Y, Tubert-Bitter P, Chaslerie A, Haramburu F. False-positives in spontaneous reporting: should we worry about them? *Br J Clin Pharmacol* 1994; **38**: 401–404.
4. Edwards IR. Adverse drug reactions: finding the needle in the haystack. *Br Med J* 1997; **315**: 500.
5. Speirs CJ. Prescription-related adverse reaction profiles and their use in risk-benefit analysis. In *Iatrogenic Diseases* (3rd ed.), D'Arcy PF, Griffin JP (eds). Oxford University Press: Oxford, 1986; 93–101.
6. Grant EM, Coulson RA, Wood SM. ADROIT and AEGIS: an IT solution to the challenge of drug safety monitoring. In *Electronic Communication Technologies-Techniques and Technologies for the 21st Century*, Mitchard M (ed.). Interpharm Press Inc.: Buffalo Grove, Illinois, 1998; 551–574.
7. Finney DJ. Systematic signalling of adverse reactions to drugs. *Meth Inf Med* 1974; **13**: 1–10.
8. Waller PC, Lee EH. Responding to drug safety issues. *Pharmacoepidemiol and Drug Safe* 1999; **8**: 535–552.

EXHIBIT C

2005 WL 3628217 (F.D.A.)

Food and Drug Administration (F.D.A.)

Center for Drug Evaluation and Research (CDER)

Center for Biologics Evaluation and Research (CBER)

GUIDANCE FOR INDUSTRY [1] GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT

March 2005

1** ***Contains Nonbinding Recommendations

TABLE OF CONTENTS

I. INTRODUCTION

II. BACKGROUND
A. PDUFA III'S RISK MANAGEMENT GUIDANCE GOAL
B. OVERVIEW OF THE RISK MANAGEMENT GUIDANCES
III. THE ROLE OF PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY IN RISK MANAGEMENT

IV. IDENTIFYING AND DESCRIBING SAFETY SIGNALS: FROM CASE REPORTS TO CASE SERIES
A. GOOD REPORTING PRACTICE
B. CHARACTERISTICS OF A GOOD CASE REPORT
C. DEVELOPING A CASE SERIES
D. SUMMARY DESCRIPTIVE ANALYSIS OF A CASE SERIES
E. USE OF DATA MINING TO IDENTIFY PRODUCT-EVENT COMBINATIONS
F. SAFETY SIGNALS THAT MAY WARRANT FURTHER INVESTIGATION
G. PUTTING THE SIGNAL INTO CONTEXT: CALCULATING REPORTING RATES VS. INCIDENCE RATES
V. BEYOND CASE REVIEW: INVESTIGATING A SIGNAL THROUGH OBSERVATIONAL STUDIES
A. PHARMACOEPIDEMIOLOGIC STUDIES
B. REGISTRIES
C. SURVEYS
VI. INTERPRETING SAFETY SIGNALS: FROM SIGNAL TO POTENTIAL SAFETY RISK

VII. BEYOND ROUTINE PHARMACOVIGILANCE: DEVELOPING A PHARMACOVIGILANCE PLAN

I. INTRODUCTION

This document provides guidance to industry on good pharmacovigilance practices and pharmacoepidemiologic assessment of observational data regarding drugs, including biological drug products (excluding blood and blood components). [2] Specifically, this document provides guidance on (1) safety signal identification, (2) pharmacoepidemiologic assessment and safety signal interpretation, and (3) pharmacovigilance plan development.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. PDUFA III's Risk Management Guidance Goal

On June 12, 2002, Congress reauthorized, for the second time, the Prescription Drug User Fee Act (PDUFA III). In the context of PDUFA III, FDA agreed to satisfy certain performance goals. One of those goals was to produce guidance for industry on risk management activities for drug and biological products. As an initial step towards satisfying that goal, FDA sought public comment on risk management. Specifically, FDA issued three concept papers. Each paper focused on one aspect of risk management, including (1) conducting premarketing risk assessment, (2) developing and implementing risk minimization tools, and (3) performing postmarketing pharmacovigilance and pharmacoepidemiologic assessments. In addition to receiving numerous written comments regarding the three concept papers, FDA held a public workshop on April 9 - 11, 2003, to discuss the concept papers. FDA considered all of the comments received in developing three draft guidance documents on risk management activities. The draft guidance documents were published on May 5, 2004, and the public was provided with an opportunity to comment on them until July 6, 2004. FDA considered all of the comments received in producing the final guidance documents.

*2 *1. Premarketing Risk Assessment (Premarketing Guidance)*

2. Development and Use of Risk Minimization Action Plans (RiskMAP Guidance)

3. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (Pharmacovigilance Guidance)

B. Overview of the Risk Management Guidances

Like the concept papers and draft guidances that preceded them, each of the three final guidance documents focuses on one aspect of risk management. The *Premarketing Guidance* and the *Pharmacovigilance Guidance* focus on premarketing and postmarketing risk assessment, respectively. The *RiskMAP Guidance* focuses on risk minimization. Together, risk assessment and risk minimization form what FDA calls *risk management*. Specifically, risk management is an iterative process of (1) assessing a product's benefit-risk balance, (2) developing and implementing tools to minimize its risks while preserving its benefits, (3) evaluating tool effectiveness and reassessing the benefit-risk balance, and (4) making adjustments, as appropriate, to the risk minimization tools to further improve the benefit-risk balance. This four-part process should be continuous throughout a product's lifecycle, with the results of risk assessment informing the sponsor's decisions regarding risk minimization.

When reviewing the recommendations provided in this guidance, sponsors and applicants should keep the following points in mind:

• Many recommendations in this guidance are ***not*** intended to be generally applicable to all products.

Industry already performs risk assessment and risk minimization activities for products during development and marketing. The Federal Food, Drug, and Cosmetic Act (FDCA) and FDA implementing regulations establish requirements for ***routine*** risk assessment and risk minimization (see e.g., FDA requirements for professional labeling, and adverse event monitoring and reporting). As a result, many of the recommendations presented here focus on situations when a product may pose a clinically important and unusual type or level of risk. To the extent possible, we have specified in the text whether a recommendation is intended for all products or only this subset of products.

• It is of critical importance to protect patients and their privacy during the generation of safety data and the development of risk minimization action plans.

During all risk assessment and risk minimization activities, sponsors must comply with applicable regulatory requirements involving human subjects research and patient privacy. [3]

• To the extent possible, this guidance conforms with FDA's commitment to harmonize international definitions and standards as appropriate.

The topics covered in this guidance are being discussed in a variety of international forums. We are participating in these discussions and believe that, to the extent possible, the recommendations in this guidance reflect current thinking on related issues.

*3 • When planning risk assessment and risk minimization activities, sponsors should consider input from health care participants likely to be affected by these activities (e.g., from consumers, pharmacists and pharmacies, physicians, nurses, and third party payers).

• There are points of overlap among the three guidances.

We have tried to note in the text of each guidance when areas of overlap occur and when referencing one of the other guidances might be useful.

III. THE ROLE OF PHARMACOVIGILANCE AND PHARMACOEPIDEMIOLOGY IN RISK MANAGEMENT

Risk assessment during product development should be conducted in a thorough and rigorous manner; however, it is impossible to identify all safety concerns during clinical trials. Once a product is marketed, there is generally a large increase in the number of patients exposed, including those with co-morbid conditions and those being treated with concomitant medical products. Therefore, postmarketing safety data collection and risk assessment based on observational data are critical for evaluating and characterizing a product's risk profile and for making informed decisions on risk minimization.

This guidance document focuses on pharmacovigilance activities in the post-approval period. This guidance uses the term *pharmacovigilance* to mean all scientific and data gathering activities relating to the detection, assessment, and understanding of adverse events. This includes the use of pharmacoepidemiologic studies. These activities are undertaken with the goal of identifying adverse events and understanding, to the extent possible, their nature, frequency, and potential risk factors.

Pharmacovigilance principally involves the identification and evaluation of safety signals. In this guidance document, *safety signal* refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from postmarketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.

IV. IDENTIFYING AND DESCRIBING SAFETY SIGNALS: FROM CASE REPORTS TO CASE SERIES

Good pharmacovigilance practice is generally based on acquiring complete data from spontaneous adverse event reports, also known as case reports. The reports are used to develop case series for interpretation.

A. Good Reporting Practice

*4 Spontaneous case reports of adverse events submitted to the sponsor and FDA, and reports from other sources, such as the medical literature or clinical studies, may generate signals of adverse effects of drugs. The quality of the reports is critical for appropriate evaluation of the relationship between the product and adverse events. FDA recommends that sponsors make a reasonable attempt to obtain complete information for case assessment during initial contacts and subsequent follow-up, especially for serious events, [4] and encourages sponsors to use trained health care practitioners to query reporters. Computer-assisted interview technology, targeted questionnaires, or other methods developed to target specific events can help focus the line of questioning. When the report is from a consumer, it is often important to obtain permission to contact the health care practitioner familiar with the patient's adverse event to obtain further medical information and to retrieve relevant medical records, as needed.

FDA suggests that the intensity and method of case follow-up be driven by the seriousness of the event reported, the report's origin (e.g., health care practitioner, patient, literature), and other factors. FDA recommends that the most aggressive follow-up efforts be directed towards serious adverse event reports, especially of adverse events not known to occur with the drug.

B. Characteristics of a Good Case Report

Good case reports include the following elements:

1. Description of the adverse events or disease experience, including time to onset of signs or symptoms;

2. Suspected and concomitant product therapy details (i.e., dose, lot number, schedule, dates, duration), including over-the-counter medications, dietary supplements, and recently discontinued medications;

3. Patient characteristics, including demographic information (e.g., age, race, sex), baseline medical condition prior to product therapy, co-morbid conditions, use of concomitant medications, relevant family history of disease, and presence of other risk factors;

4. Documentation of the diagnosis of the events, including methods used to make the diagnosis;

5. Clinical course of the event and patient outcomes (e.g., hospitalization or death); [5]

6. Relevant therapeutic measures and laboratory data at baseline, during therapy, and subsequent to therapy, including blood levels, as appropriate;

7. Information about response to dechallenge and rechallenge; and

8. Any other relevant information (e.g., other details relating to the event or information on benefits received by the patient, if important to the assessment of the event).

For reports of medication errors, good case reports also include full descriptions of the following, when such information is available:

1. Products involved (including the trade (proprietary) and established (proper) name, manufacturer, dosage form, strength, concentration, and type and size of container);

*5 2. Sequence of events leading up to the error;

3. Work environment in which the error occurred; and

4. Types of personnel involved with the error, type(s) of error, and contributing factors.

FDA recommends that sponsors capture in the case narrative section of a medication error report all appropriate information outlined in the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy. [6] Although sponsors are not required to use the taxonomy, FDA has found the taxonomy to be a useful tool to categorize and analyze reports of medication errors. It provides a standard language and structure for medication error-related data collected through reports.

C. Developing a Case Series

FDA suggests that sponsors initially evaluate a signal generated from postmarketing spontaneous reports through a careful review of the cases and a search for additional cases. Additional cases could be identified from the sponsor's global adverse event databases, the published literature, and other available databases, such as FDA's Adverse Event Reporting System (AERS) or Vaccine Adverse Events Reporting System (VAERS), using thorough database search strategies based on updated coding terminology (e.g., the Medical Dictionary for Regulatory Activities (MedDRA)). When available, FDA recommends

that standardized case definitions (i.e., formal criteria for including or excluding a case) be used to assess potential cases for inclusion in a case series.[7] In general, FDA suggests that case-level review occur before other investigations or analyses. FDA recommends that emphasis usually be placed on review of serious, unlabeled adverse events, although other events may warrant further investigation (see section IV.F. for more details).

As part of the case-level review, FDA suggests that sponsors evaluate individual case reports for clinical content and completeness, and follow up with reporters, as necessary. It is important to remove any duplicate reports. In assessing case reports, FDA recommends that sponsors look for features that may suggest a causal relationship between the use of a product and the adverse event, including:

1. Occurrence of the adverse event in the expected time (e.g., type 1 allergic reactions occurring within days of therapy, cancers developing after years of therapy);

2. Absence of symptoms related to the event prior to exposure;

3. Evidence of positive dechallenge or positive rechallenge;

4. Consistency of the event with the established pharmacological/toxicological effects of the product, or for vaccines, consistency with established infectious or immunologic mechanisms of injury;

5. Consistency of the event with the known effects of other products in the class;

6. Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiologic studies; and

***6** 7. Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medical conditions).

Confounded cases are common, especially among patients with complicated medical conditions. Confounded cases (i.e., cases with adverse events that have possible etiologies other than the product of concern) could still represent adverse effects of the product under review. FDA recommends that sponsors carefully evaluate these cases and not routinely exclude them. Separate analyses of unconfounded cases may be useful.

For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmacoepidemiologic studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.

FDA does not recommend any specific categorization of causality, but the categories *probable*, *possible*, or *unlikely* have been used previously.[8] If a causality assessment is undertaken, FDA suggests that the causal categories be specified and described in sufficient detail to understand the underlying logic in the classification.

If the safety signal relates to a medication error, FDA recommends that sponsors report all known contributing factors that led to the event. A number of references are available to assist sponsors in capturing a complete account of the event.[9] FDA recommends that sponsors follow up to the extent possible with reporters to capture a complete account of the event, focusing on the *medication use systems* (e.g., prescribing/order process, dispensing process, administration process). This data may be informative in developing strategies to minimize future errors.

D. Summary Descriptive Analysis of a Case Series

In the event that one or more cases suggest a safety signal warranting additional investigation, FDA recommends that a case series be assembled and descriptive clinical information be summarized to characterize the potential safety risk and, if possible, to identify risk factors. A case series commonly includes an analysis of the following:

1. The clinical and laboratory manifestations and course of the event;

2. Demographic characteristics of patients with events (e.g., age, gender, race);

3. Exposure duration;

4. Time from initiation of product exposure to the adverse event;

5. Doses used in cases, including labeled doses, greater than labeled doses, and overdoses;

6. Use of concomitant medications;

7. The presence of co-morbid conditions, particularly those known to cause the adverse event, such as underlying hepatic or renal impairment;

*7 8. The route of administration (e.g., oral vs. parenteral);

9. Lot numbers, if available, for products used in patients with events; and

10. Changes in event reporting rate over calendar time or product life cycle.

E. Use of Data Mining to Identify Product-Event Combinations

At various stages of risk identification and assessment, systematic examination of the reported adverse events by using statistical or mathematical tools, or so-called *data mining*, can provide additional information about the existence of an excess of adverse events reported for a product. By applying data mining techniques to large adverse event databases, such as FDA's AERS or VAERS, it may be possible to identify unusual or unexpected product-event combinations warranting further investigation. Data mining can be used to augment existing signal detection strategies and is especially useful for assessing patterns, time trends, and events associated with drug-drug interactions. Data mining is not a tool for establishing causal attributions between products and adverse events.

The methods of data mining currently in use usually generate a score comparing (1) the fraction of all reports for a particular event (e.g., liver failure) for a specific drug (i.e., the “observed reporting fraction”) with (2) the fraction of reports for the same particular event for all drugs (i.e., “the expected reporting fraction”). [10] This analysis can be refined by adjusting for aspects of reporting (e.g., the reporting year) or characteristics of the patient (e.g., age or gender) that might influence the amount of reporting. In addition, it may be possible to limit data mining to an analysis for drugs of a specific class or for drugs that are used to treat a particular disease.

The score (or statistic) generated by data mining quantifies the disproportionality between the observed and expected values for a given product-event combination. This score is compared to a threshold that is chosen by the analyst. A potential excess of adverse events is operationally defined as any product-event combination with a score exceeding the specified threshold. When applying data mining to large databases (such as AERS), it is not unusual for a product to have several product-event combinations with scores above a specified threshold. The lower the threshold, the greater the likelihood that more combinations will exceed the threshold and will warrant further investigation.

Several data mining methods have been described and may be worth considering, such as the Multi-Item Gamma Poisson Shrinker (MGPS) algorithm [11] [12] the Proportional Reporting Ratio (PRR) method [13] [14] and the Neural Network approach. [15] Except when the observed number of cases with the drug event combination is small (e.g., less than 20) or the expected number of cases with the drug event combination is < 1, the MGPS and PRR methods will generally identify similar drug event combinations for further investigation. [16]

*8 Although all of these approaches are inherently exploratory or hypothesis generating, they may provide insights into the patterns of adverse events reported for a given product relative to other products in the same class or to all other products.

FDA exercises caution when making such comparisons, because voluntary adverse event reporting systems such as AERS or VAERS are subject to a variety of reporting biases (e.g., some observations could reflect concomitant treatment, not the product itself, and other factors, including the disease being treated, other co-morbidities or unrecorded confounders, may cause the events to be reported). In addition, AERS or VAERS data may be affected by the submission of incomplete or duplicate reports, underreporting, or reporting stimulated by publicity or litigation. As reporting biases may differ by product and change over time, and could change differently for different events, it is not possible to predict their impact on data mining scores.

Use of data mining techniques is not a required part of signal identification or evaluation. If data mining results are submitted to FDA, they should be presented in the larger appropriate clinical epidemiological context. This should include (1) a description of the database used, (2) a description of the data mining tool used (e.g., statistical algorithm, and the drugs, events and stratifications selected for the analyses) or an appropriate reference, and (3) a careful assessment of individual case reports and any other relevant safety information related to the particular drug-event combination of interest (e.g., results from preclinical, clinical, pharmacoepidemiologic, or other available studies).

F. Safety Signals That May Warrant Further Investigation

FDA believes that the methods described above will permit a sponsor to identify and preliminarily characterize a safety signal. The actual risk to patients cannot be known from these data because it is not possible to characterize all events definitively and because there is invariably under-reporting of some extent and incomplete information about duration of therapy, numbers treated, etc. Safety signals that may warrant further investigation may include, but are not limited to, the following:

1. New unlabeled adverse events, especially if serious;

2. An apparent increase in the severity of a labeled event;

3. Occurrence of serious events thought to be extremely rare in the general population;

4. New product-product, product-device, product-food, or product-dietary supplement interactions;

5. Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities);

6. Confusion about a product's name, labeling, packaging, or use;

7. Concerns arising from the way a product is used (e.g., adverse events seen at higher than labeled doses or in populations not recommended for treatment);

*9 8. Concerns arising from potential inadequacies of a currently implemented risk minimization action plan (e.g., reports of serious adverse events that appear to reflect failure of a RiskMAP goal); [17] and

9. Other concerns identified by the sponsor or FDA.

G. Putting the Signal into Context: Calculating Reporting Rates vs. Incidence Rates

If a sponsor determines that a concern about an excess of adverse events or safety signal warrants further investigation and analysis, it is important to put the signal into context. For this reason, calculations of the rate at which new cases of adverse events occur in the product-exposed population (i.e., the incidence rate) are the hallmark of pharmacoepidemiologic risk assessment.

In pharmacoepidemiologic studies (see section V.A), the numerator (number of new cases) and denominator (number of exposed patients and time of exposure or, if known, time at risk) may be readily ascertainable. In contrast, for spontaneously reported events, it is not possible to identify all cases because of under-reporting, and the size of the population at risk is at best an estimate. Limitations in national denominator estimates arise because:

1. Accurate national estimates of the number of patients exposed to a medical product and their duration of exposure may not be available;

2. It may be difficult to exclude patients who are not at risk for an event, for example, because their exposure is too brief or their dose is too low; [18] and

3. A product may be used in different populations for different indications, but use estimates are not available for the specific population of interest.

Although we recognize these limitations, we recommend that sponsors calculate crude adverse event reporting rates as a valuable step in the investigation and assessment of adverse events. FDA suggests that sponsors calculate reporting rates by using the total number of spontaneously reported cases in the United States in the numerator and estimates of national patient exposure to product in the denominator. [19] [20] FDA recommends that whenever possible, the number of patients or person time exposed to the product nationwide be the estimated denominator for a reporting rate. FDA suggests that other surrogates for exposure, such as numbers of prescriptions or kilograms of product sold, only be used when patient-level estimates are unavailable. FDA recommends that sponsors submit a detailed explanation of the rationale for selection of a denominator and a method of estimation.

Comparisons of reporting rates and their temporal trends can be valuable, particularly across similar products or across different product classes prescribed for the same indication. However, such comparisons are subject to substantial limitations in interpretation because of the inherent uncertainties in the numerator and denominator used. As a result, FDA suggests that a comparison of two or more reporting rates be viewed with extreme caution and generally considered exploratory or hypothesis-generating. Reporting rates can by no means be considered incidence rates, for either absolute or comparative purposes.

***10** To provide further context for incidence rates or reporting rates, it is helpful to have an estimate of the background rate of occurrence for the event being evaluated in the general population or, ideally, in a subpopulation with characteristics similar to that of the exposed population (e.g., premenopausal women, diabetics). These background rates can be derived from: (1) national health statistics, (2) published medical literature, or (3) ad hoc studies, particularly of subpopulations, using large automated databases or ongoing epidemiologic investigations with primary data collection. FDA suggests that comparisons of incidence rates or reporting rates to background rate estimates take into account potential differences in the data sources, diagnostic criteria, and duration of time at risk.

While the extent of under-reporting is unknown, it is usually assumed to be substantial and may vary according to the type of product, seriousness of the event, population using the product, and other factors. As a result, a reporting rate higher than the background rate may, in some cases, be a strong indicator that the true incidence rate is sufficiently high to be of concern. However, many other factors affect the reporting of product-related adverse events (e.g., publicity, newness of product to the market) and these factors should be considered when interpreting a high reporting rate. Also, because of under-reporting, the fact that a reporting rate is less than the background rate does not necessarily show that the product is not associated with an increased risk of an adverse event.

V. BEYOND CASE REVIEW: INVESTIGATING A SIGNAL THROUGH OBSERVATIONAL STUDIES

FDA recognizes that there are a variety of methods for investigating a safety signal. Signals warranting additional investigation can be further evaluated through carefully designed non-randomized observational studies of the product's use in the “real world” and randomized trials. The *Premarketing Guidance* discusses a number of types of randomized trials, including the large simple safety study, which is a risk assessment method that could be used either pre- or post-approval.

This document focuses on three types of non-randomized observational studies: (1) pharmacoepidemiologic studies, (2) registries, and (3) surveys. By focusing this guidance on certain risk assessment methods, we do not intend to advocate the use of these approaches over others. FDA encourages sponsors to consider all methods to evaluate a particular safety signal. FDA recommends that sponsors choose the method best suited to the particular signal and research question of interest. Sponsors planning to evaluate a safety signal are encouraged to communicate with FDA as their plans progress.

A. Pharmacoepidemiologic Studies

Pharmacoepidemiologic studies can be of various designs, including cohort (prospective or retrospective), case-control, nested case-control, case-crossover, or other models.[21] The results of such studies may be used to characterize one or more safety signals associated with a product, or may examine the natural history of a disease or drug utilization patterns. Unlike a case series, a pharmacoepidemiologic study which is designed to assess the risk attributed to a drug exposure has a protocol and control group and tests prespecified hypotheses. Pharmacoepidemiologic studies can allow for the estimation of the relative risk of an outcome associated with a product, and some (e.g., cohort studies) can also provide estimates of risk (incidence rate) for an adverse event. Sponsors can initiate pharmacoepidemiologic studies at any time. They are sometimes started at the time of initial marketing, based on questions that remain after review of the premarketing data. More often, however, they are initiated when a safety signal has been identified after approval. Finally, there may also be occasions when a pharmacoepidemiologic study is initiated prior to marketing (e.g., to study the natural history of disease or patterns of product use, or to estimate background rates for adverse events).

***11** For uncommon or delayed adverse events, pharmacoepidemiologic studies may be the only practical choice for evaluation, even though they can be limited by low statistical power. Clinical trials are impractical in almost all cases when the event rates of concern are less common than 1:2000-3000 (an exception may be larger trials conducted for some vaccines, which could move the threshold to 1:10,000). It may also be difficult to use clinical trials: (1) to evaluate a safety signal associated with chronic exposure to a product, exposure in populations with co-morbid conditions, or taking multiple concomitant medications, or (2) to identify certain risk factors for a particular adverse event. On the other hand, for evaluation of more common events, which are seen relatively often in untreated patients, clinical trials may be preferable to observational studies.

Because pharmacoepidemiologic studies are observational in nature, they may be subject to confounding, effect modification, and other bias, which may make results of these types of studies more difficult to interpret than the results of clinical trials. Some of these problems can be surmounted when the relative risk to exposed patients is high.

Because different products pose different benefit-risk considerations (e.g., seriousness of the disease being treated, nature and frequency of the safety signal under evaluation), it is impossible to delineate a universal set of criteria for the point at which a pharmacoepidemiologic study should be initiated, and the decision should be made on a case-by-case basis. When an important adverse event-product association leads to questions on the product's benefit-risk balance, FDA recommends that sponsors consider whether the particular signal should be addressed with one or more pharmacoepidemiologic studies. If a sponsor determines that a pharmacoepidemiologic study is the best method for evaluating a particular signal, the design and size of the proposed study would depend on the objectives of the study and the expected frequency of the events of interest.

When performing a pharmacoepidemiologic study, FDA suggests that investigators seek to minimize bias and to account for possible confounding. Confounding by indication is one example of an important concern in performing a pharmacoepidemiologic study.[22] Because of the effects of bias, confounding, or effect modification, pharmacoepidemiologic studies evaluating the same hypothesis may provide different or even conflicting results. It is almost always prudent to conduct more than one study, in more than one environment and even use different designs. Agreement of the results from more than one study helps to provide reassurance that the observed results are robust.

There are a number of references describing methodologies for pharmacoepidemiologic studies, discussing their strengths and limitations,[23] and providing guidelines to facilitate the conduct, interpretation, and documentation of such studies.[24] Consequently, this guidance document does not comprehensively address these topics. However, a protocol for a pharmacoepidemiologic study generally includes:

***12** 1. Clearly specified study objectives;

2. A critical review of the literature; and

3. A detailed description of the research methods, including:

• the population to be studied;

• the case definitions to be used;

• the data sources to be used (including a rationale for data sources if from outside the U.S.);

• the projected study size and statistical power calculations; and

• the methods for data collection, management, and analysis.

Depending on the type of pharmacoepidemiologic study planned, there are a variety of data sources that may be used, ranging from the prospective collection of data to the use of existing data, such as data from previously conducted clinical trials or large databases. In recent years, a number of pharmacoepidemiologic studies have been conducted in automated claims databases (e.g., HMO, Medicaid) that allow retrieval of records on product exposure and patient outcomes. In addition, recently, comprehensive electronic medical record databases have also been used for studying drug safety issues. Depending on study objectives, factors that may affect the choice of databases include the following:

1. Demographic characteristics of patients enrolled in the health plans (e.g., age, geographic location);

2. Turnover rate of patients in the health plans;

3. Plan coverage of the medications of interest;

4. Size and characteristics of the exposed population available for study;

5. Availability of the outcomes of interest;

6. Ability to identify conditions of interest using standard medical coding systems (e.g., International Classification of Diseases (ICD-9)), procedure codes or prescriptions that could be used as markers;

7. Access to medical records; and

8. Access to patients for data not captured electronically.

For most pharmacoepidemiologic studies, FDA recommends that sponsors validate diagnostic findings through a detailed review of at least a sample of medical records. If the validation of the specific outcome or exposure of interest using the proposed database has been previously reported, FDA recommends that the literature supporting the validity of the proposed study be submitted for review.

FDA encourages sponsors to communicate with the Agency when pharmacoepidemiologic studies are being developed.

B. Registries

The term *registry* as used in pharmacovigilance and pharmacoepidemiology can have varied meanings. In this guidance document, a registry is “an organized system for the collection, storage, retrieval, analysis, and dissemination of information on individual persons exposed to a specific medical intervention who have either a particular disease, a condition (e.g., a risk factor) that predisposes [them] to the occurrence of a health-related event, or prior exposure to substances (or circumstances) known or suspected to cause adverse health effects.” [25] Whenever possible, a control or comparison group should be included, (i.e., individuals with a disease or risk factor who are not treated or are exposed to medical interventions other than the intervention of interest). [26]

***13** Through the creation of registries, a sponsor can evaluate safety signals identified from spontaneous case reports, literature reports, or other sources, and evaluate factors that affect the risk of adverse outcomes, such as dose, timing of exposure, or patient characteristics. [27] Registries can be particularly useful for:

1. Collecting outcome information not available in large automated databases; and

2. Collecting information from multiple sources (e.g., physician records, hospital summaries, pathology reports, vital statistics), particularly when patients receive care from multiple providers over time.

A sponsor can initiate a registry at any time. It may be appropriate to initiate the registry at or before initial marketing, when a new indication is approved, or when there is a need to evaluate safety signals identified from spontaneous case reports. In deciding whether to establish a registry, FDA recommends that a sponsor consider the following factors:

1. The types of additional risk information desired;

2. The attainability of that information through other methods; and

3. The feasibility of establishing the registry.

Sponsors electing to initiate a registry should develop written protocols that provide: (1) objectives for the registry, (2) a review of the literature, and (3) a summary of relevant animal and human data. FDA suggests that protocols also contain detailed descriptions of: (1) plans for systematic patient recruitment and follow-up, (2) methods for data collection, management, and analysis, and (3) conditions under which the registry will be terminated. A registry-based monitoring system should include carefully designed data collection forms to ensure data quality, integrity, and validation of registry findings against a sample of medical records or through interviews with health care providers. FDA recommends that the size of the registry and the period during which data will be collected be consistent with the safety questions under study and we encourage sponsors to discuss their registry development plans with FDA.

C. Surveys

Patient or health care provider surveys can gather information to assess, for example:

1. A safety signal;

2. Knowledge about labeled adverse events;

3. Use of a product as labeled, particularly when the indicated use is for a restricted population or numerous contraindications exist;

4. Compliance with the elements of a RiskMAP (e.g., whether or not a Medication Guide was provided at the time of product dispensing); and [28]

5. Confusion in the practicing community over sound-alike or look-alike trade (or proprietary) names.

Like a registry, a survey can be initiated by a sponsor at any time. It can be conducted at the time of initial marketing (i.e., to fulfill a postmarketing commitment) or when there is a desire to evaluate safety signals identified from spontaneous case reports.

***14** FDA suggests that sponsors electing to initiate a survey develop a written protocol that provides objectives for the survey and a detailed description of the research methods, including: (1) patient or provider recruitment and follow-up, (2) projected sample size, and (3) methods for data collection, management, and analysis. [29] FDA recommends that a survey-based monitoring system include carefully designed survey instruments and validation of survey findings against a sample of medical or pharmacy records or through interviews with health care providers, whenever possible. FDA recommends that survey instruments be validated or piloted before implementation. FDA suggests that sponsors consider whether survey translation and cultural validation would be important.

Sponsors are encouraged to discuss their survey development plans with FDA.

VI. INTERPRETING SAFETY SIGNALS: FROM SIGNAL TO POTENTIAL SAFETY RISK

After identifying a safety signal, FDA recommends that a sponsor conduct a careful case level review and summarize the resulting case series descriptively. To help further characterize a safety signal, a sponsor can also: (1) employ data mining techniques, and (2) calculate reporting rates for comparison to background rates. Based on these findings and other available data (e.g., from preclinical or other sources), FDA suggests that a sponsor consider further study (e.g., observational studies) to establish whether or not a potential safety risk exists.

When evaluation of a safety signal suggests that it may represent a potential safety risk, FDA recommends that a sponsor submit a synthesis of all available safety information and analyses performed, ranging from preclinical findings to current observations. This submission should include the following:

1. Spontaneously reported and published case reports, with denominator or exposure information to aid interpretation;

2. Background rate for the event in general and specific patient populations, if available;

3. Relative risks, odds ratios, or other measures of association derived from pharmacoepidemiologic studies;

4. Biologic effects observed in preclinical studies and pharmacokinetic or pharmacodynamic effects;

5. Safety findings from controlled clinical trials; and

6. General marketing experience with similar products in the class.

After the available safety information is presented and interpreted, it may be possible to assess the degree of causality between use of a product and an adverse event. FDA suggests that the sponsor's submission provide an assessment of the benefit-risk balance of the product for the population of users as a whole and for identified at-risk patient populations, and, if appropriate, (1) propose steps to further investigate the signal through additional studies, and (2) propose risk minimization actions. [30] FDA will make its own assessment of the potential safety risk posed by the signal in question, taking into account the information provided by the sponsor and any additional relevant information known to FDA (e.g., information on other products in the same class) and will communicate its conclusions to the sponsor whenever possible. Factors that are typically considered include:

***15** 1. Strength of the association (e.g., relative risk of the adverse event associated with the product);

2. Temporal relationship of product use and the event;

3. Consistency of findings across available data sources;

4. Evidence of a dose-response for the effect;

5. Biologic plausibility;

6. Seriousness of the event relative to the disease being treated;

7. Potential to mitigate the risk in the population;

8. Feasibility of further study using observational or controlled clinical study designs; and

9. Degree of benefit the product provides, including availability of other therapies.

As noted in section II, risk management is an iterative process and steps to further investigate a potential safety risk, assess the product's benefit-risk balance, and implement risk minimization tools would best occur in a logical sequence, not simultaneously. Not all steps may be recommended, depending on the results of earlier steps. [31] FDA recommends that

assessment of causality and of strategies to minimize product risk occur on an ongoing basis, taking into account the findings from newly completed studies.

VII. BEYOND ROUTINE PHARMACOVIGILANCE: DEVELOPING A PHARMACOVIGILANCE PLAN

For most products, routine pharmacovigilance (i.e., compliance with applicable postmarket requirements under the FDCA and FDA implementing regulations) is sufficient for postmarketing risk assessment. However, in certain limited instances, unusual safety risks may become evident before approval or after a product is marketed that could suggest that consideration by the sponsor of a pharmacovigilance plan may be appropriate. A pharmacovigilance plan is a plan developed by a sponsor that is focused on detecting new safety risks and/or evaluating already identified safety risks. Specifically, a pharmacovigilance plan describes pharmacovigilance efforts above and beyond routine postmarketing spontaneous reporting, and is designed to enhance and expedite the sponsor's acquisition of safety information.[32] The development of pharmacovigilance plans may be useful at the time of product launch or when a safety risk is identified during product marketing. FDA recommends that a sponsor's decision to develop a pharmacovigilance plan be based on scientific and logistical factors, including the following:

1. The likelihood that the adverse event represents a potential safety risk;

2. The frequency with which the event occurs (e.g., incidence rate, reporting rate, or other measures available);

3. The severity of the event;

4. The nature of the population(s) at risk;

5. The range of patients for which the product is indicated (broad range or selected populations only); and

6. The method by which the product is dispensed (through pharmacies or performance linked systems only).[33]

A pharmacovigilance plan may be developed by itself or as part of a Risk Minimization Action Plan (RiskMAP), as described in the *RiskMAP Guidance*. Sponsors may meet with representatives from the appropriate Office of New Drugs review division and the Office of Drug Safety in CDER, or the appropriate Product Office and the Division of Epidemiology, Office of Biostatistics and Epidemiology in CBER regarding the specifics of a given product's pharmacovigilance plan.

***16** FDA believes that for a product without safety risks identified pre- or post-approval and for which at-risk populations are thought to have been adequately studied, routine spontaneous reporting will be sufficient for postmarketing surveillance. On the other hand, pharmacovigilance plans may be appropriate for products for which: (1) serious safety risks have been identified pre- or post-approval, or (2) at-risk populations have not been adequately studied. Sponsors may discuss with the Agency the nature of the safety concerns posed by such a product and the determination whether a pharmacovigilance plan is appropriate.

A pharmacovigilance plan could include one or more of the following elements:

1. Submission of specific serious adverse event reports in an expedited manner beyond routine required reporting (i.e., as 15-day reports);

2. Submission of adverse event report summaries at more frequent, prespecified intervals (e.g., quarterly rather than annually);

3. Active surveillance to identify adverse events that may or may not be reported through passive surveillance. Active surveillance can be (1) drug based: identifying adverse events in patients taking certain products, (2) setting based: identifying adverse events in certain health care settings where they are likely to present for treatment (e.g., emergency departments, etc.), or (3) event based: identifying adverse events that are likely to be associated with medical products (e.g., acute liver failure);

4. Additional pharmacoepidemiologic studies (for example, in automated claims databases or other databases) using cohort, case-control, or other appropriate study designs (see section V);

5. Creation of registries or implementation of patient or health care provider surveys (see section V); and

6. Additional controlled clinical trials. [34]

As data emerges, FDA recommends that a sponsor re-evaluate the safety risk and the effectiveness of its pharmacovigilance plan. Such re-evaluation may result in revisions to the pharmacovigilance plan for a product. In some circumstances, FDA may decide to bring questions on potential safety risks and pharmacovigilance plans before its Drug Safety and Risk Management Advisory Committee or the FDA Advisory Committee dealing with the specific product in question. Such committees may be convened when FDA seeks: (1) general advice on the design of pharmacoepidemiologic studies, (2) comment on specific pharmacoepidemiology studies developed by sponsors or FDA for a specific product and safety question, or (3) advice on the interpretation of early signals from a case series and on the need for further investigation in pharmacoepidemiologic studies. While additional information is being developed, sponsors working with FDA can take interim actions to communicate information about potential safety risks (e.g., through labeling) to minimize the risk to users of the product.

1 This guidance has been prepared by the PDUFA III Pharmacovigilance Working Group, which includes members from the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.
Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
or
Office of Communication, Training, and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
March 2005
Clinical Medical

2 For ease of reference, this guidance uses the term *product* or *drug* to refer to all products (excluding blood and blood components) regulated by CDER and CBER. Similarly, for ease of reference, this guidance uses the term *approval* to refer to both drug approval and biologic licensure.
Paperwork Reduction Act Public Burden Statement: This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (PRA) (44 U.S.C. 3501-3520). The collection(s) of information in this guidance were approved under OMB Control No. 0910-0001 (until March 31, 2005) and 0910-0338 (until August 31, 2005).

3 See 45 CFR part 46 and 21 CFR parts 50 and 56. See also the Health Insurance Portability and Accountability Act of 1996 (HIPAA) (Public Law 104-191) and the Standards for Privacy of Individually Identifiable Health Information (the Privacy Rule) (45 CFR part 160 and subparts A and E of part 164). The Privacy Rule specifically permits covered entities to report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products both to manufacturers and directly to

FDA (45 CFR 164.512(b)(1)(i) and (iii), and 45 CFR 164.512(a)(1)). For additional guidance on patient privacy protection, see http://www.hhs.gov/ocr/hipaa.

4 Good reporting practices are extensively addressed in a proposed FDA regulation and guidance documents. See (1) Safety Reporting Requirements for Human Drug and Biological Products, Proposed Rule, 68 FR 12406 (March 14, 2003), (2) FDA guidance for industry on *Postmarketing Reporting of Adverse Experiences*, (3) FDA guidance for industry on *E2C Clinical Safety Data Management: Periodic Safety Update Report (PSUR)*, (4) FDA guidance for industry on *Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products: Clarification of What to Report*.

5 Patient outcomes may not be available at the time of initial reporting. In these cases, follow-up reports can convey important information about the course of the event and serious outcomes, such as hospitalization or death.

6 See http://www.nccmerp.org for the definition of a medication error and taxonomy of medication errors.

7 See, for example, Institute of Medicine (IOM) Immunization Safety Review on Vaccines and Autism, 2004.

8 See World Health Organization, the Uppsala Monitoring Center, 2000, *Safety Monitoring of Medicinal Product*, for additional categorizations of causality.

9 See Cohen MR (ed), 1999, *Medication Errors*, American Pharmaceutical Association, Washington DC; Cousins DD (ed), 1998, *Medication Use: A Systems Approach to Reducing Errors*, Joint Commission on Accreditation of Healthcare Organizations, Oakbrook Terrace, IL.

10 Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

11 DuMouchel W and Pregibon D, 2001, Empirical Bayes screening for multi-item associations, *Seventh ACM SigKDD International Conference on Knowledge Discovery and Data Mining*.

12 Szarfman A, Machado SG, and O'Neill RT, 2002, Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database, *Drug Safety* 25(6): 381-92.

13 Evans SJW, Waller P, and Davis S, 1998, Proportional reporting ratios: the uses of epidemiological methods for signal generation [abstract], *Pharmacoepidemiology and Drug Safety* 7:S102.

14 Evans SJ, 2000, Pharmacovigilance: A science or fielding emergencies? *Statistics in Medicine* 19(23):3199-209; Evans SJW, Waller PC, and Davis S, 2001, Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports, *Pharmacoepidemiology and Drug Safety* 10:483-6.

15 Bate A et al., 1998, A Bayesian neural network method for adverse drug reaction signal generation, *European Journal of Clinical Pharmacology* 54:315-21.

16 This conclusion is based on the experience of FDA and of William DuMouchel, Ph.D., Chief Scientist, Lincoln Technologies, Wellsley, MA, as summarized in an email communication from Dr. DuMouchel to Ana Szarfman, M.D., Ph.D., Medical Officer, OPaSS, CDER, on October 13, 2004.

17 For a detailed discussion of risk minimization action plan evaluation, please consult the *RiskMAP Guidance*.

18 See *Current Challenges in Pharmacovigilance: Pragmatic Approaches*, Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group V, Geneva, 2001.

19 See Rodriguez EM, Staffa JA, Graham DJ, 2001, *The role of databases in drug postmarketing surveillance*, Pharmacoepidemiology and Drug Safety, 10:407-10.

20 In addition to U.S. reporting rates, sponsors can provide global reporting rates, when relevant.

21 *Guidelines for Good Pharmacoepidemiology*,, International Society for Pharmacoepidemiology, 2004 (http:// www.pharmacoepi.org/resources/guidelines_ 08027.cfm)

22 See, for example, Strom BL (ed), 2000, *Pharmacoepidemiology*, 3rd edition, Chichester: John Wiley and Sons, Ltd; Hartzema AG, Porta M, and Tilson HH (eds), 1998, *Pharmacoepidemiology*: *An Introduction*, 3rd edition, Cincinnati, OH: Harvey Whitney Books.

23 Ibid.

24 *Guidelines for Good Pharmacoepidemiology*, International Society for Pharmacoepidemiology, 2004 (http://www.pharmacoepi.org/ resources/guidelines_ 08027.cfm).

25 See Frequently Asked Questions About Medical and Public Health Registries, The National Committee on Vital and Health Statistics, at http:// www.ncvhs.hhs.gov.

26 See for example, FDA Guidance for Industry, *Establishing Pregnancy Exposure Registries*, August 2002 http://www.fda.gov/cder/ guidance/3626fnl.pdf.

27 Ibid.

28 For a detailed discussion of RiskMAP evaluation, please consult the *RiskMAP Guidance*.

29 See 21 CFR parts 50 and 56 for FDA's regulations governing the protection of human subjects.

30 In the vast majority of cases, risk communication that incorporates appropriate language into the product's labeling will be adequate for risk minimization. In rare instances, however, a sponsor may consider implementing a RiskMAP. Please refer to the *RiskMAP Guidance* for a complete discussion of RiskMAP development.

31 For additional discussion of the relationship between risk assessment and risk minimization, please consult the *RiskMAP Guidance*.

32 As used in this document, the term “pharmacovigilance plan” is defined differently than in the ICH draft E2E document (version 4.1). As used in the ICH document, a “pharmacovigilance plan” would be routinely developed (i.e., even when a sponsor does not anticipate that enhanced pharmacovigilance efforts are necessary). In contrast, as discussed above, FDA is only recommending that pharmacovigilance plans be developed when warranted by unusual safety risks. This ICH guidance is available on the Internet at http:// www.fda.gov/cder/guidance/index.htm under the topic ICH Efficacy. The draft E2E guidance was made available on March 30, 2004 (69 FR 16579). ICH agreed on the final version of the E2E guidance in November, 2004.

33 For a detailed discussion of controlled access systems, please consult the *RiskMAP Guidance*.

34 For a discussion of risk assessment in controlled clinical trials, please consult the *Premarketing Guidance*.

End of Document

EXHIBIT D

2005 WL 3628208 (F.D.A.)

Food and Drug Administration (F.D.A.)

Center for Drug Evaluation and Research (CDER)

Center for Biologics Evaluation and Research (CBER)

GUIDANCE FOR INDUSTRY [1] E2E PHARMACOVIGILANCE PLANNING

April 2005

1** **Contains Nonbinding Recommendations

TABLE OF CONTENTS

I. INTRODUCTION (1, 1.1)
A. Background (1.2)
B. Scope of the Guidance (1.3)
II. SAFETY SPECIFICATION (2)
A. Elements of the Specification (2.1)
1. Nonclinical (2.1.1)
2. Clinical (2.1.2)
B. Summary (2.2)
III. PHARMACOVIGILANCE PLAN (3)
A. Structure of the Pharmacovigilance Plan (3.1)
1. Summary of Ongoing Safety Issues (3.1.1)
2. Routine Pharmacovigilance Practices (3.1.2)
3. Action Plan for Safety Issues (3.1.3)
4. Summary of Actions To Be Completed, Including Milestones (3.1.4)
B. Pharmacovigilance Methods (3.2)
IV. REFERENCES (4)

ANNEX -- PHARMACOVIGILANCE METHODS

I. INTRODUCTION (1, 1.1) [2]

This guidance is intended to aid in planning pharmacovigilance activities, especially in preparation for the early postmarketing period of a new drug (in this guidance, the term *drug* denotes chemical entities, biotechnology-derived products, and vaccines). The main focus of this guidance is on a safety specification and pharmacovigilance plan that might be submitted at the time of license application. The guidance can be used by sponsors to develop a stand-alone document for regions that prefer this approach or to provide guidance on incorporation of elements of the safety specification and pharmacovigilance plan into the Common Technical Document (CTD).

The guidance describes a method for summarizing the important identified risks of a drug, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied preapproval. It proposes a structure for a pharmacovigilance plan and sets out principles of good practice for the design and conduct of observational studies. It does not describe other methods to reduce risks from drugs, such as risk communication. The guidance takes into consideration ongoing work in the three regions and beyond on these issues.

This guidance does not cover the entire scope of pharmacovigilance. It uses the World Health Organization (WHO) definition of the term *pharmacovigilance* as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems." This definition encompasses the use of pharmacoepidemiological studies.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

A. Background (1.2)

*2 The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient characteristics and the number of patients exposed. In particular, during the early postmarketing period, the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe.

Once a product is marketed, new information will be generated, which can have an impact on the benefits or risks of the product; evaluation of this information should be a continuing process, in consultation with regulatory authorities. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use. The benefit-risk balance can be improved by reducing risks to patients through effective pharmacovigilance that can enable information feedback to the users of medicines in a timely manner.

Industry and regulators have identified the need for better and earlier planning of pharmacovigilance activities before a product is approved or a license is granted. This ICH guidance has been developed to encourage harmonization and consistency and prevent duplication of effort and could be of benefit to public health programs throughout the world as they consider new drugs in their countries.

B. Scope of the Guidance (1.3)

The guidance could be most useful for new chemical entities, biotechnology-derived products, and vaccines, as well as for significant changes in established products (e.g., new dosage form, new route of administration, or new manufacturing process for a biotechnology-derived product) and for established products that are to be introduced to new populations or in significant new indications or where a new major safety concern has arisen.

The purpose of this guidance is to propose a structure for a pharmacovigilance plan and a safety specification that summarizes the identified and potential risks of the product to be addressed in the plan. The guidance is divided into the following sections:

• Safety specification

• Pharmacovigilance plan

• Annex -- Pharmacovigilance Methods

It is recommended that company pharmacovigilance experts get involved early in product development. Planning and dialogue with regulators should also start long before license application. A safety specification and pharmacovigilance plan can also be developed for products already on the market (e.g., new indication or major new safety concern). The plan could be used as the basis for discussion of pharmacovigilance activities with regulators in the different ICH regions and beyond.

For products with important identified risks, important potential risks or important missing information, the pharmacovigilance plan should include additional actions designed to address these concerns. For products for which no special concerns have arisen, routine pharmacovigilance as described in section III.A.2 (3.1.2) of this guidance should be sufficient for postapproval safety monitoring, without the need for additional actions (e.g., safety studies).

*3 During the course of implementing the various components of the plan, any important emerging benefit or risk information should be discussed and used to revise the plan.

The following principles underpin this guidance:

• Planning of pharmacovigilance activities throughout the product life-cycle

• Science-based approach to risk documentation

• Effective collaboration between regulators and industry

• Applicability of the pharmacovigilance plan across the three ICH regions

II. SAFETY SPECIFICATION (2)

The safety specification should be a summary of the important identified risks of a drug, important potential risks, and important missing information. It should also address the populations potentially at-risk (where the product is likely to be used), and outstanding safety questions that warrant further investigation to refine understanding of the benefit-risk profile during the postapproval period. This safety specification is intended to help industry and regulators identify any need for specific data collection and also to facilitate the construction of the pharmacovigilance plan. The safety specification can be built initially during the premarketing phase and, at the time approval is sought, it should reflect the status of issues that were being followed during development.

The Common Technical Document (CTD), especially the Overview of Safety (2.5.5), Benefits and Risks Conclusions (2.5.6), and the Summary of Clinical Safety (2.7.4) sections, includes information relating to the safety of the product and should be the basis of the safety issues identified in the safety specification. Sponsors should support the safety specification with references to specific pages of the CTD or other relevant documents. The safety specification can be a stand-alone document, usually in conjunction with the pharmacovigilance plan, but elements can also be incorporated into the CTD. The length of the document will generally depend on the product and its development program. Appendices can be added if it is considered important to provide a more detailed explanation of important risks or analyses.

A. Elements of the Safety Specification (2.1)

It is recommended that sponsors follow the structure of elements provided below when compiling the safety specification. The elements of the safety specification that are included are only a guide. The safety specification can include additional elements, depending on the nature of the product and its development program. Conversely, for products already on the market with emerging new safety concerns, only a subset of the elements might be relevant.

The focus of the safety specification should be on the identified risks, important potential risks, and important missing information. The following elements should be considered for inclusion.

1. Nonclinical (2.1.1)

Within the Specification, this section should present nonclinical safety findings that have not been adequately addressed by clinical data, for example:

*4 • Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity, etc.)

• General pharmacology (cardiovascular, including QT interval prolongation; nervous system; etc.)

• Drug interactions

• Other toxicity-related information or data

If the product is intended for use in special populations, consideration should be given to whether specific nonclinical data needs exist.

2. Clinical (2.1.2)

a. Limitations of the human safety database

Limitations of the safety database (e.g., related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Particular reference should be made to populations likely to be exposed during the intended or expected use of the product in medical practice.

The worldwide experience should be briefly discussed, including:

• The extent of the worldwide exposure

• Any new or different safety issues identified

• Any regulatory actions related to safety

b. Populations not studied in the preapproval phase

The specification should discuss which populations have not been studied or have only been studied to a limited degree in the preapproval phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed (CTD 2.5.5). Populations to be considered should include (but might not be limited to):

• Children

• The elderly

• Pregnant or lactating women

• Patients with relevant co-morbidity such as hepatic or renal disorders

• Patients with disease severity different from that studied in clinical trials

• Sub-populations carrying known and relevant genetic polymorphism

• Patients of different racial and/or ethnic origins

c. Adverse events (AEs)/adverse drug reactions (ADRs)

This section should list the important identified and potential risks that require further characterization or evaluation. Specific references should be made to guide a reviewer to where clinical safety data are presented (e.g., relevant sections of the CTD 2.5.5 and 2.7.4). Discussion of risk factors and potential mechanisms that apply to identified AEs/ADRs should draw on information from any part of the CTD (nonclinical and clinical) and other relevant information, such as other drug labels, scientific literature, and postmarketing experience.

Identified risks for further evaluation

More detailed information should be included on the most important identified AEs/ADRs, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the product. This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available. Risk factors and potential mechanisms should be discussed. These AEs/ADRs should usually call for further evaluation as part of the pharmacovigilance plan (e.g., frequency in normal conditions of use, severity, outcome, at-risk groups).

Potential risks for further evaluation

*5 Important potential risks should be described in this section. The evidence that led to the conclusion that there was a potential risk should be presented. It is anticipated that for any important potential risk, there should be further evaluation to characterize the association.

d. Identified and potential interactions, including food-drug and drug-drug interactions

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. For each, the evidence supporting the interaction and possible mechanism should be summarized, and the potential health risks posed for the different indications and in the different populations should be discussed.

e. Epidemiology

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should take into account whenever possible stratification by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed (because the epidemiology of the indication(s) may vary across regions), if this information is available.

In addition, for important adverse events that may require further investigation, it is useful to review the incidence rates of these events among patients in whom the drug is indicated (i.e., the background incidence rates). For example, if condition X is an important adverse event in patients who are treated with drug Y for disease Z, then it is useful to review the incidence of condition X in patients with disease Z who are not treated with drug Y; this is the background rate of condition X among patients with disease Z. Information on risk factors for an adverse event (condition X) would also be useful to include, if available.

f. Pharmacological class effects

The safety specification should identify risks believed to be common to the pharmacological class.

B. Summary (2.2)

At the end of the safety specification, a summary should be provided of the:

• Important identified risks

• Important potential risks

• Important missing information

Sponsors are encouraged to summarize specific ongoing safety issues on an issue-by-issue basis, including both nonclinical and clinical data that are pertinent to the problem.

III. PHARMACOVIGILANCE PLAN (3)

This section gives guidance on the structure of a pharmacovigilance plan. The pharmacovigilance plan should be based on the safety specification. The specification and plan can be written as two parts of the same document. The plan would normally be developed by the sponsor and can be discussed with regulators during product development, prior to approval (i.e., when the marketing application is submitted) of a new product, or when a safety concern arises postmarketing. It can be a stand-alone document, but elements could also be incorporated into the CTD.

For products for which no special concerns have arisen, routine pharmacovigilance as described in section III.A.2 (3.1.2) of this guidance should be sufficient for postapproval safety monitoring, without the need for additional actions (e.g., safety studies). However, for products with important identified risks, important potential risks, or important missing information, additional actions designed to address these concerns should be considered.

*6 The length of the document will likely depend on the product and its development program. The pharmacovigilance plan should be updated as important information on safety becomes available and milestones are reached.

A. Structure of the Pharmacovigilance Plan (3.1)

Outlined below is a suggested structure for the pharmacovigilance plan. The structure can be varied depending on the product in question and the issues identified in the safety specification.

1. Summary of Ongoing Safety Issues (3.1.1)

At the beginning of the pharmacovigilance plan, a summary should be provided of the:

• Important identified risks

• Important potential risks

• Important missing information

This is important if the pharmacovigilance plan is a separate document from the safety specification.

2. Routine Pharmacovigilance Practices (3.1.2)

Routine pharmacovigilance should be conducted for all medicinal products, regardless of whether or not additional actions are appropriate as part of a pharmacovigilance plan. This routine pharmacovigilance should include the following:

• Systems and processes that ensure that information about all suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner

• The preparation of reports for regulatory authorities:

-- Expedited adverse drug reaction (ADR) reports

-- Periodic safety update reports (PSURs)

• Continuous monitoring of the safety profile of approved products including signal detection, issue evaluation, updating of labeling, and liaison with regulatory authorities

• Other requirements, as defined by local regulations

In some ICH regions, there might be a regulatory requirement to present within the pharmacovigilance plan an overview of the company's organization and practices for conducting pharmacovigilance. In the absence of such a requirement, a statement that the company's routine pharmacovigilance practices include the elements outlined in the bulleted list above should be sufficient.

3. Action Plan for Safety Issues (3.1.3)

The plan for each important safety issue should be presented and justified according to the following structure:

• Safety issue

• Objective of proposed action(s)

• Action(s) proposed

• Rationale for proposed action(s)

• Monitoring by the sponsor for safety issue and proposed action(s)

• Milestones for evaluation and reporting

Any protocols for specific studies can be provided in the CTD section 5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., Module 4 if the study is a nonclinical study).

4. Summary of Actions To Be Completed, Including Milestones (3.1.4)

An overall pharmacovigilance plan for the product bringing together the actions for all individual safety issues should be presented. Whereas section 3.1.3 suggests presenting an action plan by ongoing safety issue, for this section the pharmacovigilance plan for the product should be organized in terms of the actions to be undertaken and their milestones. The reason for this is that one proposed action (e.g., a prospective safety cohort study) could address more than one of the identified issues.

***7** It is recommended that milestones for completion of studies and other evaluations, and for submission of safety results, be included in the pharmacovigilance plan. In developing these milestones, one should consider when:

• Exposure to the product will have reached a level sufficient to allow potential identification/characterization of the AEs/ADRs of concern or resolution of a particular concern, and/or

• The results of ongoing or proposed safety studies are expected to be available.

These milestones might be aligned with regulatory milestones (e.g., PSURs, annual reassessment and license renewals) and used to revise the pharmacovigilance plan.

B. Pharmacovigilance Methods (3.2)

The best method to address a specific situation can vary, depending on the product, the indication, the population being treated and the issue to be addressed. The method chosen can also depend on whether an identified risk, potential risk, or missing information is the issue and whether signal detection, evaluation, or safety demonstration is the main objective of further study. When choosing a method to address a safety concern, sponsors should employ the most appropriate design. The Annex provides a summary of the key methods used in pharmacovigilance. This is provided to aid sponsors considering possible methods to address specific issues identified by the safety specification. This list is not all-inclusive, and sponsors should use the most up-to-date methods that are relevant and applicable.

Design and Conduct of Observational Studies (3.2.1)

Carefully designed and conducted pharmacoepidemiological studies, specifically observational (noninterventional, nonexperimental) studies, are important tools in pharmacovigilance. In observational studies, the investigator “observes and evaluates results of ongoing medical care without ‘controlling’ the therapy beyond normal medical practice.” [1]

Before the observational study that is part of a pharmacovigilance plan commences, a protocol should be finalized. Experts from relevant disciplines (e.g., pharmacovigilance experts, pharmacoepidemiologists and biostatisticians) should be consulted. It is recommended that the protocol be discussed with the regulatory authorities before the study starts. It is also suggested that the circumstances in which a study should be terminated early be discussed with regulatory authorities and documented in advance. A study report after completion, and interim reports if appropriate, should be submitted to the authorities according to the milestones within the pharmacovigilance plan.

Study protocols should, as a minimum, include the study aims and objectives, the methods to be used, and the plan for analysis. The final study report should accurately and completely present the study objectives, methods, results, and the principal investigator's interpretation of the findings.

***8** It is recommended that the sponsor follow good epidemiological practice for observational studies and also internationally accepted guidelines, such as the guidelines endorsed by the International Society for Pharmacoepidemiology. [2] In some of the ICH regions, local laws and guidelines also apply to the design and conduct of observational studies and should be followed.

The highest possible standards of professional conduct and confidentiality should always be maintained, and any relevant national legislation on data protection followed.

IV. REFERENCES (4)

1 CIOMS, Current Challenges in Pharmacovigilance: Pragmatic Approaches. Report of CIOMS Working Group V. Geneva; World Health Organization (WHO), 2001.

2 Guidelines for Good Pharmacoepidemiology Practices (GPP), International Society for Pharmacoepidemiology, http://www.pharmacoepi.org/resources/guidelines_08027.cfm, August 2004.

ANNEX -- PHARMACOVIGILANCE METHODS

1. Passive Surveillance

• Spontaneous Reports

A spontaneous report is an unsolicited communication by healthcare professionals or consumers to a company, regulatory authority or other organization (e.g., WHO, regional centers, poison control center) that describes one or more adverse drug reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme. [1]

Spontaneous reports play a major role in the identification of safety signals once a drug is marketed. In many instances, a company can be alerted to rare adverse events that were not detected in earlier clinical trials or other premarketing studies. Spontaneous reports can also provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions. Caution should be exercised in evaluating spontaneous reports, especially when comparing drugs. The data accompanying spontaneous reports are often incomplete, and the rate at which cases are reported is dependent on many factors including the time since launch, pharmacovigilance-related regulatory activity, media attention, and the indication for use of the drug. [2 3 4 5]

Systematic Methods for the Evaluation of Spontaneous Reports

More recently, systematic methods for the detection of safety signals from spontaneous reports have been used. Many of these techniques are still in development and their usefulness for identifying safety signals is being evaluated. These methods include the calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection. [6 7 8] Data mining techniques have also been used to examine drug-drug interactions. [9] Data mining techniques should always be used in conjunction with, and not in place of, analyses of single case reports. Data mining techniques facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation. This tool does not quantify the magnitude of risk, and caution should be exercised when comparing drugs. Further, when using data mining techniques, consideration should be given to the threshold established for detecting signals, since this will have implications for the sensitivity and specificity of the method (a high threshold is associated with high specificity and low sensitivity). Confounding factors that influence spontaneous adverse event reporting are not removed by data mining. Results of data mining should be interpreted with the knowledge of the weaknesses of the spontaneous reporting system and, more specifically, the large differences in the ADR reporting rate among different drugs and the many potential biases inherent in spontaneous reporting. All signals should be evaluated recognizing the possibility of false positives. In addition, the absence of a signal does not mean that a problem does not exist.

• Case Series

*9 Series of case reports can provide evidence of an association between a drug and an adverse event, but they are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome. There are certain distinct adverse events known to be associated more frequently with drug therapy, such as anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens-Johnson Syndrome. [10 11] Therefore, when events such as these are spontaneously reported, sponsors should place more emphasis on these reports for detailed and rapid follow-up.

2. Stimulated Reporting

Several methods have been used to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods. [12] Such methods include on-line reporting of adverse events and systematic stimulation of reporting of adverse events based on a predesigned method. Although these methods have been shown to improve reporting, they are not devoid of the limitations of passive surveillance, especially selective reporting and incomplete information.

During the early postmarketing phase, companies might actively provide health professionals with safety information, and at the same time encourage cautious use of new products and the submission of spontaneous reports when an adverse event is identified. A plan can be developed before the product is launched (e.g., through site visits by company representatives, by direct mailings or faxes, etc.). Stimulated adverse event reporting in the early postmarketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population (e.g., Early Post-marketing Phase Vigilance, EPPV in Japan). This should be regarded as a form of spontaneous event reporting; thus, data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated.

3. Active Surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain completely the number of adverse events via a continuous preorganized process. An example of active surveillance is the follow-up of patients treated with a particular drug through a risk management program. Patients who fill a prescription for this drug may be asked to complete a brief survey form and give permission for later contact. [13] In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system.

• Sentinel Sites

Active surveillance can be achieved by reviewing medical records or interviewing patients and/or physicians in a sample of sentinel sites to ensure complete and accurate data on reported adverse events from these sites. The selected sites can provide information, such as data from specific patient subgroups, that would not be available in a passive spontaneous reporting system. Further, information on the use of a drug, such as abuse, can be targeted at selected sentinel sites. [14] Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Active surveillance with sentinel sites is most efficient for those drugs used mainly in institutional settings such as hospitals, nursing homes, hemodialysis centers, etc. Institutional settings can have a greater frequency of use for certain drug products and can provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings can provide an efficient active surveillance system. Intensive monitoring of sentinel sites can also be helpful in identifying risks among patients taking orphan drugs.

• Drug Event Monitoring

***10** Drug event monitoring is a method of active pharmacovigilance surveillance. In drug event monitoring, patients might be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at prespecified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire. [12] [15] [16] [17] Limitations of drug event monitoring can include poor physician and patient response rates and the unfocused nature of data collection, which can obscure important signals. In addition, maintenance of patient confidentiality might be a concern. On the other hand, more detailed information on adverse events from a large number of physicians and/or patients might be collected.

• Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic can be a disease (disease registry) or a specific exposure (drug registry). Both types of registries, which only differ by the type of patient data of interest, can collect a battery of information using standardized questionnaires in a prospective fashion. Disease registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations can help collect data on drug exposure and other

factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients with another condition within the registry, or patients outside the registry.

Exposure (drug) registries address populations exposed to drugs of interest (e.g., registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a drug has a special impact on this group of patients. Some exposure (drug) registries address drug exposures in specific populations, such as pregnant women. Patients can be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies can measure incidence, but, without a comparison group, cannot provide proof of association. However, they can be useful for signal amplification, particularly for rare outcomes. This type of registry can be very valuable when examining the safety of an orphan drug indicated for a specific condition.

4. Comparative Observational Studies

Traditional epidemiologic methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports or case series. Major types of these designs are cross-sectional studies, case-control studies, and cohort studies (both retrospective and prospective). [12] [15]

• Cross-sectional Study (Survey)

***11** Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed. These studies are best used to examine the prevalence of a disease at one time point or to examine trends over time, when data for serial time points can be captured. These studies can also be used to examine the crude association between exposure and outcome in ecologic analyses. Cross-sectional studies are best utilized when exposures do not change over time.

• Case-control Study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease in the two groups. Patients can be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls can be stratified according to the population of interest (the elderly, children, pregnant women, etc.). For rare adverse events, existing large population-based databases are a useful and efficient means of providing needed drug exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a drug (or drugs) and one specific rare adverse event, as well as to identify risk factors for adverse events. Risk factors can include conditions such as renal and hepatic dysfunction, that might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study can provide the absolute incidence rate of the event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, an incidence rate can be calculated.

• Cohort Study

In a cohort study, a population-at-risk for the disease (or event) is followed over time for the occurrence of the disease (or event). Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a drug at one time during follow-up, but nonexposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving drug exposure, comparison cohorts of interest are selected on the basis of drug use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. Multiple adverse events can also be investigated using the same data source in a cohort study. However, it can be difficult to recruit sufficient numbers of patients who are exposed

to a drug of interest (such as an orphan drug) or to study very rare outcomes. Like case-control studies, the identification of patients for cohort studies can come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies can be used to examine safety issues in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist.

***12** There are several automated databases available for pharmacoepidemiologic studies.[12 15 18] They include databases that contain automated medical records or automated accounting/billing systems. Databases that are created from accounting/billing systems might be linked to pharmacy claims and medical claims databases. These datasets might include millions of patients. Since they are created for administrative or billing purposes, they might not have the detailed and accurate information needed for some research, such as validated diagnostic information or laboratory data. Although medical records can be used to ascertain and validate test results and medical diagnoses, one should be cognizant of the privacy and confidentiality regulations that apply to patient medical records.

5. Targeted Clinical Investigations

When significant risks are identified from preapproval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction can put patients at an increased risk of adverse events. Genetic testing can also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the drug in general practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies can include population pharmacokinetic studies and drug concentration monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from preapproval clinical trials, but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include the elderly, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolize drugs differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

To elucidate the benefit-risk profile of a drug outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event, a large simplified trial might be conducted. Patients enrolled in a large simplified trial are usually randomized to avoid selection bias. In this type of trial, though, the event of interest will be focused to ensure a convenient and practical study. One limitation of this method is that the outcome measure might be too simplified and this might have an impact on the quality and ultimate usefulness of the trial. Large, simplified trials are also resource-intensive.

6. Descriptive Studies

***13** Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with drug exposures. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of drugs in specified populations.

• Natural History of Disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest, can be used to assist in putting spontaneous reports into perspective.[15] For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.

• Drug Utilization Study

Drug utilization studies (DUS) describe how a drug is marketed, prescribed, and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. [12] These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication, and other characteristics. DUS can be used to determine if a product is being used in these populations. From these studies denominator data can be developed for use in determining rates of adverse drug reactions. DUS have been used to describe the effect of regulatory actions and media attention on the use of drugs, as well as to develop estimates of the economic burden of the cost of drugs. DUS can be used to examine the relationship between recommended and actual clinical practice. These studies can help to determine whether a drug has the potential for drug abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. Important limitations of these studies can include a lack of clinical outcome data or information of the indication for use of a product.

REFERENCES

3 Faich GA, U.S. adverse drug reaction surveillance 1989 - 1994. Pharmacoepidemiology Drug Safety 1996; 393-398.

4 Goldman SA, Limitations and strengths of spontaneous reports data. Clinical Therapeutics 1998; 20 (Suppl C):C40-C44.

5 Hartmann K, Doser AK, Kuhn M, Postmarketing safety information: How useful are spontaneous reports. Pharmacoepidemiology and Drug Safety 1999; 8:S65-S71.

6 “Responding to Signals” Waller PC and Arlett PA, in Pharmacovigilance, Editor Mann RD, John Wiley and Sons Ltd 2002.

7 DuMouchel W, Bayesian data mining in large frequency tables, with an application to the FDA Spontaneous Reporting system. Am Stat 1999; 53:177-190.

8 Bate A, Lindquist M, Edwards IR, A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacology 1998; 54:315-321.

9 Van Puijenbroek E, Egberts ACG, Heerdink ER, Leufkens HGM, Detecting drug-drug interactions using a database for spontaneous adverse drug reactions: An example with diuretics and non-steroidal anti-inflammatory drugs. Eur J Clin Pharmacol 2000; 56:733-738.

10 Venning GR, Identification of adverse reactions to new drugs. III: Alerting processes and early warning systems. BMJ 1983; 286:458-460.

11 Edwards IR, The management of adverse drug reactions: From diagnosis to signal. Thérapie 2001; 56:727-733.

12 In Strom BL (ed.). Pharmacoepidemiology, 3rd ed. 2002; John Wiley and Sons, Ltd, New York, NY.

13 Mitchell AA, Van Bennekom CM, Louik C, A pregnancy-prevention program in women of childbearing age receiving isotretinoin. N Engl J Med (1995 Jul 13); 333(2):101-6.

14 Task Force on Risk Management. Report to the FDA Commissioner. Managing the risks from medical product use: Creating a risk management framework. Part 3. How does FDA conduct postmarketing surveillance and risk assessment. May 1999.

15 In Mann RD and Andrews EB (eds.) Pharmacovigilance 2002, John Wiley and Sons, Ltd, West Sussex, England.

16 Coulter DM, The New Zealand intensive medicines monitoring programme in pro-active safety surveillance. Pharmacoepidemiology and Drug Safety 2000; 9:273-280.

17 Mackay FJ, Post-marketing studies. The work of the Drug Safety Research Unit. Drug Safety 1998;19: 343-353.

18 Garcia Rodriguez LA, Perez Gutthann S, Use of the UK General Practice Research Database for Pharmacoepidemiology. Br. J Clin Pharmacol 1998; 45:419-425.

Footnotes

1 ICH Guidance E2D; Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting, 3.1.1 Spontaneous Reports.

2 Pinkston V, Swain EJ, Management of adverse drug reactions and adverse event data through collection, storage, and retrieval. In Stephens MDB, Talbot JCC, and Routledge PA, eds. Detection of New Adverse Drug Reactions. 4th ed. 1998; MacMillan Reference Ltd, London. p 282.

1 This guidance was developed within the Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and has been subject to consultation by the regulatory parties, in accordance with the ICH process. This document has been endorsed by the ICH Steering Committee at *Step 4* of the ICH process, November 2004. At *Step 4* of the process, the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan, and the United States.

Additional copies are available from:
Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
http://www.fda.gov/cder/guidance/index.htm
Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
http://www.fda.gov/cber/guidelines.htm.
(Tel) Voice Information System at 800-835-4709 or 301-827-1800
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
April 2005
ICH

2 Arabic numbers reflect the organizational breakdown in the document endorsed by the ICH Steering Committee at Step 4 of the ICH process, November 2004.

End of Document

EXHIBIT E

COMMENTARY

Potential for Conflict of Interest in the Evaluation of Suspected Adverse Drug Reactions

A Counterpoint

Brian L. Strom, MD, MPH

HEALTH CARE PRACTITIONERS AND PATIENTS SEEK safe and effective drugs. However, no drug is completely safe; all drugs have toxic effects that must be balanced with their benefits in deciding whether they should be marketed or used in any given person. To inform such decisions, the United States relies on a drug approval system whereby preclinical studies precede 3 phases of clinical studies. Collectively, these usually include 500 to 3000 exposed patients and 2 or more confirmatory trials, demonstrating before marketing that a drug is effective and reasonably safe for its recommended use.[1] Thus, adverse reactions occurring in 1% or more of exposed patients are usually well described upon marketing. However, rarer adverse reactions are not well characterized until after marketing.[2] This reflects a deliberate societal decision to balance delays in access to new drugs with delays in information about rare adverse reactions. To provide the missing information, the United States maintains a postmarketing surveillance system including passive collection of spontaneous reports of adverse drug reactions (ADRs) to generate signals of possible adverse drug events. This is supplemented by formal pharmacoepidemiology studies testing those hypotheses, confirming or disproving potential signals from the spontaneous reporting system (SRS).[2]

Cerivastatin uniquely challenged this system. It is now well known that cerivastatin, when combined with gemfibrozil, poses an increased risk of rhabdomyolysis. In fact, a rhabdomyolysis warning was included in the original cerivastatin label upon its US launch, along with a warning against use with fibrates, based on experiences with previously released statins. Postmarketing reports of rhabdomyolysis soon after marketing were therefore neither unexpected nor alarming. Thus, the normally difficult decision to act more aggressively on spontaneous reports, always subjective, was even more difficult here. I share the concern by Psaty et al[3] that drug manufacturers have an inherent conflict of interest in making such decisions. However, cerivastatin presents a unique opportunity to highlight SRS limitations, and its potential misuse, and provides insights into how to improve the US drug monitoring program. This commentary will not consider issues of the ongoing litigation, including manufacturer conduct, timelines of company memos, the litany of legal exhibits, or the accusations made by Psaty et al regarding those issues. Rather, it will discuss the scientific and policy issues raised by Psaty et al, describe the SRS in some detail, and discuss appropriate uses of SRS data and organizational implications of its limitations. Cerivastatin serves as an instructive example. The company response addresses the cerivastatin legal issues elsewhere in this issue.

See also pp 2585, 2622, 2647, 2655, and 2658.

Spontaneous Reporting System

Description. The identification of possible ADRs after marketing relies on spontaneous voluntary reporting to industry or regulators of reactions observed in clinical practice, fundamentally a 1950s-era approach.[2] The Food and Drug Administration (FDA) receives approximately 280 000 such reports annually, consolidating them into a large database.[2] Few reports (<10%) are submitted directly to the FDA by health care practitioners and consumers. Rather, manufacturers receive more than 90% of reports and must then process, analyze, and report to the FDA all ADRs reported to them after use of their products.

A major advantage of the SRS is that it incorporates all drugs, prescribers, dispensers, and patients, casting the

Author Affiliations: Departments of Biostatistics and Epidemiology, Medicine, and Pharmacology, Center for Clinical Epidemiology and Biostatistics, Center for Education and Research on Therapeutics, University of Pennsylvania School of Medicine, Philadelphia.
Financial Disclosure appears at the end of this article.
Corresponding Author: Brian L. Strom, MD, MPH, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, 824 Blockley Hall, 423 Guardian Dr, Philadelphia, PA 19104-6021 (bstrom@cceb.med.upenn.edu).

broadest possible net to capture events. However, this system is subject to underascertainment (not recognizing an event is due to a drug) and overascertainment (erroneously ascribing an adverse event to a drug). Furthermore, it is subject to vast underreporting, with published reporting rates ranging from substantially below 1%[4] to 53%,[5] and variations depending on event severity and acuteness, for example. Reporting is somewhat more complete for newer or more recently marketed drugs than older drugs. External events (eg, letters to the editor in a medical journal or lay newspaper, increased suspicion about a drug's risk, or "Dear Doctor" letters) can easily modify ascertainment or reporting rates.

To calculate true ADR rates, one needs an accurate number of events in the exposed population (numerator) and an accurate number of exposed individuals (denominator). The SRS has neither. There is no true numerator because it is unclear how many ADRs actually occurred in a specific population. Accurate denominators likewise are unavailable; sponsors and the FDA know the sales of a given drug but often lack the number of individuals exposed over time. Furthermore, sponsors and the FDA do not know the number of people who used the drug and whose ADRs would have been reported had they experienced such an event, which would be the correct denominator for a numerator consisting of only reported cases.

The SRS focuses on detecting unknown adverse effects from individual new drugs; consequently, it is not adept at identifying medical adversity from recognized ADRs due to drug misuse, underprescribing, overprescribing, and other medication errors, although these affect public health more than previously unidentified rare adverse effects.[2] Nevertheless, this system remains the primary and best method for identifying ADRs to newly marketed drugs.

Appropriate Use of SRS Data. To quote the FDA, "Because of these limitations, AE [ADR] reports are primarily useful for hypothesis generating, rather than hypothesis testing."[6] Indeed, the SRS generates numerous hypotheses, many of which are neither investigated further nor confirmed. To transmit information about these untested hypotheses to patients or health care practitioners would be extremely misleading, as many are untrue. This contrasts sharply with the clinical trials referred to by Psaty et al,[3] where recently there have been calls for complete public disclosure of results of all such trials. I agree and would expand this call to include results of all pharmacoepidemiology studies. However, such trials and studies are designed to test hypotheses, which is not the purpose of the SRS.

In analyzing ADR data, Psaty et al[3] used a measure increasingly utilized by regulators in pharmacoepidemiology. The authors estimated a "relative reporting ratio," analogous to the more commonly used term *proportional reporting ratio* (PRR), which is the relative frequency of reports of a specific event compared with all events reported for a specific drug, divided by the corresponding quantity for other drugs. These "disproportionality measures" were developed to help identify signals to be explored in subsequent controlled studies and have recently been reviewed in the field's journal.[7-14] However, these exercises are formal statistical analyses of poor, incomplete, and biased data (ie, spontaneously reported adverse reactions). No matter how sophisticated, analyses of such data can readily be misleading. The controversial nature of these measures stems from the underlying data—spontaneous ADR reports—which are "only the suspicions of doctors and clinicians."[7] The various biases that affect such data can easily affect different drugs differently, leading to unequal reporting and incorrect results if SRS data are used to compare among drugs. More sophisticated analyses cannot correct for the huge imperfections in the data source. Pharmacoepidemiologists hope that using PRRs will allow for earlier hypothesis generation, although this goal still remains to be evaluated rigorously. The major role of PRRs, though, remains hypothesis generation. Indeed, some pharmacoepidemiologists question whether disproportionality analyses ever merit publication, as " . . . anecdotal case reports and disproportionality measures of them are of the same essence, and distinct from controlled epidemiologic studies."[8]

If one cannot draw conclusions from PRRs, what is the appropriate response when a "signal" of a possible problem is detected? With rare exceptions, the appropriate response is further investigation via formal epidemiological study. Deciding if and when a signal requires such study is, however, subjective. As Psaty et al note, a manufacturer has an inherent conflict of interest in making such a judgment. This underlies their concern.

The events surrounding cerivastatin are instructive. As Psaty et al indicate, a signal emerged from the SRS. One could argue whether the signal was responded to quickly enough, but neither these authors nor I were part of that decision process. Although "hindsight is 20/20," such decisions can be hard to make while events are still unfolding. However, appropriate responses did occur, including labeling changes, "Dear Doctor" letters, and ultimately drug withdrawal. If the manufacturer had succeeded in eliminating the concurrent use of cerivastatin and gemfibrozil, as it attempted, the number of affected patients likely would have been dramatically smaller. The manufacturer also launched a formal pharmacoepidemiology study,[15] presented and published in abstract form in mid-2002, confirming in a large managed care database an increased risk associated with cerivastatin when combined with gemfibrozil. The FDA, accessing the same SRS data, conducted its own analysis,[16] similar to Psaty et al. Describing the market withdrawal of cerivastatin in a 2002 letter to the editor, the FDA authors acknowledged, "Rigorous comparisons between drugs that are based on these data are not recommended, since many factors can affect reporting and an unknown number of cases may not be attributed to the drug or reported to the FDA. Reporting rates are not incidence rates."[16] The FDA also launched its own

formal pharmacoepidemiology comparative study using 11 managed care databases. Presented and published in abstract form in mid-2004, the study indicated increased risks with the use of both gemfibrozil and cerivastatin, and a marked synergy between them.[17]

Organizational Implications

What lessons can be drawn from these experiences? First, patients and health care practitioners must recognize that regulatory approval does not guarantee safety. By design, premarketing studies are limited in size and duration; postmarketing monitoring remains critical. Second, new drugs must be tracked closely following marketing to identify any new adverse effects previously undetected. This responsibility currently falls mainly to the drug's manufacturer. Third, given manufacturers' inherent conflicts of interest, adequate oversight of their decisions is necessary. Such responsibility falls to the FDA, recently strengthened in this regard with resources from the 2002 reauthorization of the Prescription Drug User Fee Act.[2]

Do critical gaps remain? Unfortunately, they do. Currently, attention focuses on whether to approve (or withdraw) new drugs. No organization primarily focuses on monitoring effects of older drugs.[2] Yet it is well recognized that old drugs, used poorly, are responsible for most public health damage caused by ADRs.[2] Furthermore, no organization is formally responsible for developing new methods for pharmacoepidemiology (eg, faster and more systematic approaches to hypothesis generation), evaluating new methods for pharmacoepidemiology research (like PRRs), conducting pharmacoepidemiology studies for which results cannot be suppressed, training scientists in disciplines needed to conduct such research, or educating health care practitioners and recipients of prescription drugs about their effects. No organization is charged with formalizing and testing decision rules for when signals from the SRS should be acted on, and how. Analogously, no organization is charged with developing and testing new methods for improving physicians' use of drugs in clinical practice.

The closest the United States has to such an organization are the 7 Centers for Education and Research in Therapeutics (CERTs), based in academic centers and funded by the Agency for Healthcare Research and Quality (AHRQ).[18] These activities are central to the mission of the CERTs. However, the fiscal year 2004 budget for the entire CERTs program is $5.8 million (L. Bosco, MD, written communication, AHRQ, August 2004). This is meager when contrasted with the more than $800 million spent developing a single new drug,[19] the $33.2 billion pharmaceutical industry expenditure in 2003 on research and development,[19] the $15.7 billion pharmaceutical industry expenditure on promotion in 2000,[20] or the more than $40 billion expected to be spent annually on the new Medicare drug benefit.[21] The Joint Commission on Prescription Drug Use, triggered by Senator Edward Kennedy, called for creating a private nonprofit Center for Drug Surveillance to address these gaps; that call came in 1980.[22] Twenty-four years later, I join Psaty et al in renewing that call. This could be accomplished by vastly increasing the number of CERTs and the funding of each. It also could be accomplished by forming a new organization. Regardless, such investment is critical to optimizing the health outcomes resulting from the substantial sums spent in the United States on therapeutics.

Conclusions

The United States spends $122 billion annually on pharmaceuticals,[23] and some researchers place fatal ADRs between the fourth and sixth leading causes of death.[24] According to a 1990 study by the US General Accounting Office, 51% of approved drugs have serious adverse effects undetected before approval.[25] All patients and physicians seek safer drugs, and safer drug usage. Yet the resources expended to ensure drug safety are extraordinarily limited. The central problem is not rare adverse reactions to new drugs, albeit these are what attract attention, resources, and litigation. Although hindsight always raises questions about whether a problem could have been detected earlier, the events surrounding cerivastatin serve as a clear example of how the system should work. Although rhabdomyolysis was already an established adverse effect of statins, a signal was seen that the rate might be even higher with this statin, and actions were taken, informed by a formal pharmacoepidemiology study mounted early by the manufacturer and, later, a larger study by the FDA. However, there is indeed a conflict of interest in asking industry to monitor its own drugs.

It is imperative, therefore, that the FDA continue to be bolstered, both in its efforts to monitor drug safety and in its new risk management initiatives.[2] In my opinion, there is no need for additional duplicative regulatory oversight of newly marketed drugs; our FDA colleagues can be trusted to do the job, given sufficient resources. However, it is also critical that the nation commit to adequately funding CERTs, a Center for Drug Surveillance, or some analogous structure, to complement the regulatory mission of the FDA. This would significantly enhance the capacity of the field to respond to such concerns and improve the speed and quality of that response.

Financial Disclosure: Dr Strom has been a consultant to most of the major pharmaceutical manufacturers, including manufacturers of other statins, and the US Food and Drug Administration, serving as a member of its Drug Safety and Risk Management Advisory Committee. He has also served as an expert witness in many product liability cases, both for and against pharmaceutical manufacturers. In particular, Dr Strom has been retained by defense attorneys as an expert in cases related to cerivastatin and rhabdomyolysis, many of which are still under active litigation. In that capacity, he has been and continues to be compensated for reviewing the epidemiological aspects of that issue and providing his expert opinion, as well as reviewing documents and depositions, including documents under court protective orders. In contrast, this commentary is written as a scientific document, based solely on published literature and Dr Strom's experience in this field. This article was written without the participation of the attorneys representing the manufacturer of cerivastatin. There was no compensation sought or obtained from the

sponsor or its attorneys, to Dr Strom directly or to his university, for the time spent in the preparation of this article. The time and effort expended on this article was in his capacity as a professor at the University of Pennsylvania School of Medicine, where he receives support from many sources, some private but mostly public, including among them the Centers for Education and Research in Therapeutics program funded by the Agency for Healthcare Quality and Research.
Acknowledgment: I am most grateful for comments on drafts of this commentary by John Farrar, MD, MSCE, PhD; Robert Gross, MD, MSCE; Sean Hennessy, PharmD, MSCE, PhD; Stephen Kimmel, MD, MSCE; Judith Kinman, MA; Ebbing Lautenbach, MD, MPH, MSCE; and Rita Schinnar, MPA.

REFERENCES

1. Strom BL. What is pharmacoepidemiology? In: Strom BL, ed. *Pharmacoepidemiology*. 3rd ed. Sussex, England: John Wiley & Sons; 2000:3-15.
2. Centers for Education and Research on Therapeutics (CERTs) Risk Assessment Workshop Participants. Risk assessment of drugs, biologics and therapeutic devices: present and future issues. *Pharmacoepidemiol Drug Saf*. 2003;12:653-662.
3. Psaty BM, Furberg CD, Ray WA, Weiss NS. Potential for conflict of interest in the evaluation of suspected adverse drug reactions: use of cerivastatin and risk of rhabdomyolysis. *JAMA*. 2004;292:2622-2631.
4. Graham DJ, Waller PC, Kurz X. A view from regulatory agencies. In: Strom BL, ed. *Pharmacoepidemiology*. 3rd ed. New York, NY: John Wiley & Sons; 2000: 109-124.
5. Heeley E, Riley J, Layton D, Wilton LV, Shakir SA. Prescription-event monitoring and reporting of adverse drug reactions. *Lancet*. 2001;358:1872-1873.
6. Kennedy DL, Goldman SA, Lillie RB. Spontaneous reporting in the United States. In: Strom BL, ed *Pharmacoepidemiology*. 3rd ed. New York, NY: John Wiley & Sons; 2000:151-174.
7. Mann RD. Assessments of disproportionality. *Pharmacoepidemiol Drug Saf*. 2004; 13:501-502.
8. Hennessy S. Disproportionality analyses of spontaneous reports. *Pharmacoepidemiol Drug Saf*. 2004;13:503-504.
9. Zhou W, Pool V, DeStefano F, Iskander JK, Haber P, Chen RT; the VAERS Working Group. A potential signal of Bell's palsy after parenteral inactivated influenza vaccines: reports to the Vaccine Adverse Event Reporting System (VAERS)—United States, 1991-2001. *Pharmacoepidemiol Drug Saf*. 2004;13:505-510.
10. Shapiro S. Clinical judgment, common sense and adverse reaction reporting. *Pharmacoepidemiol Drug Saf*. 2004;13:511-513.
11. Zhou W, Pool V, DeStefano F, Iskander JK, Haber P, Chen RT. Reply to the editorial. *Pharmacoepidemiol Drug Saf*. 2004;13:515-517.
12. Rothman KJ, Lanes S, Sacks ST. The reporting odds ratio and its advantages over the proportional reporting ratio. *Pharmacoepidemiol Drug Saf*. 2004;13:519-523.
13. Waller P, van Puijenbroek E, Egberts A, Evans S. The reporting odds ratio versus the proportional reporting ratio: "deuce." *Pharmacoepidemiol Drug Saf*. 2004; 13:525-526.
14. Rothman KJ, Lanes S, Sacks ST. Measuring drug effects means getting a clearer signal. *Pharmacoepidemiol Drug Saf*. 2004;13:527-528.
15. Yu-Isenberg KS, Chang EY, Faich GA, White TJ. Incidence of myopathy after statin drug use: a comparative cohort study [abstract]. *Pharmacoepidemiol Drug Saf*. 2002;11(suppl 1):S180.
16. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med*. 2002;346:539-540.
17. Graham DJ, Staffa JA, Schech SD, et al. Incidence of severe myopathy and rhabdomyolysis following use of HMG-CoA reductase inhibitors or fibrates. *Pharmacoepidemiol Drug Saf*. 2004;13(suppl 1):S250-S251.
18. Califf RM; the Centers for Education and Research on Therapeutics. The need for a national infrastructure to improve the rational use of therapeutics. *Pharmacoepidemiol Drug Saf*. 2002;11:319-327.
19. Pharmaceutical Research and Manufacturers of America. *Pharmaceutical Industry Profile 2004*. Washington, DC: Pharmaceutical Research and Manufacturers of America; 2004.
20. Rosenthal MB, Berndt ER, Donohue JM, Frank RG, Epstein AM. Promotion of prescription drugs to consumers. *N Engl J Med*. 2002;346:498-505.
21. Iglehart JK. The new Medicare prescription-drug benefit: a pure power play. *N Engl J Med*. 2004;350:826-833.
22. *Report of the Joint Commission on Prescription Drug Use: Final Report.* Rockville, Md: Joint Commission on Prescription Drug Use Inc; 1980.
23. Fischer MA, Avorn J. Potential savings from increased use of generic drugs in the elderly: what the experience of Medicaid and other insurance programs means for a Medicare drug benefit. *Pharmacoepidemiol Drug Saf*. 2004;13:207-214.
24. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279:1200-1205.
25. US General Accounting Office. *FDA Drug Review: Postapproval Risks 1876-85.* Washington, DC: US General Accounting Office; 1990:24. Publication GAO/PEMD-90-15.

EXHIBIT F

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2003; **12**: 271–281
Published online 22 April 2003 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pds.848

ORIGINAL REPORT

Biases affecting the proportional reporting ratio (PRR) in spontaneous reports pharmacovigilance databases: the example of sertindole

Nicholas Moore[1]*, Gillian Hall[2], Miriam Sturkenboom[3], Ron Mann[4], Rajaa Lagnaoui[1] and Bernard Begaud[1]

[1]*Département de Pharmacologie, Université Victor Segalen-Bordeaux 2, Bordeaux, France*
[2]*E-mail: gillian.hall@gchall.demon.co.uk*
[3]*Departments of Epidemiology and Biostatistics and Medical Informatics, Erasmus University Medical Centre, Rotterdam, The Netherlands*
[4]*Professor Emeritus, Southampton University. E-mail: DrMann@manorcottage.fsbusiness.co.uk*

SUMMARY

Background Automated measures of reporting disproportionality in databases of spontaneous reports of adverse drug reactions are an emerging tool to identify drug-related alerts. Sertindole, a new atypical neuroleptic known to prolong the QT interval, was suspended in November 1998 because the proportion of reports of fatal reactions suggesting arrhythmia among all reports with sertindole was almost ten times higher than that for other atypical neuroleptics in the UK. This excess risk was not predicted in preclinical data and had not been found in premarketing trials.

Method Reporting patterns over time were analysed. Prescription Event Monitoring (PEM) studies and a large retrospective cohort allowed for the comparison of actual death rates with atypical neuroleptics, and to assess which proportion of the deaths that occurred were reported.

Results There were indications of possible skewing of reporting related to notoriety, surveillance and market size effects. Death rates in PEM studies were essentially similar between sertindole and other neuroleptics. Cardiac deaths had been two to three times more often reported than other causes of death.

Conclusion Proportional reporting ratios indicate differential reporting of possible reactions, not necessarily differential occurrence. There was no indication of an actual increase of risk of all causes or cardiac deaths during sertindole treatment, but only an increased risk of its being reported. The suspension of sertindole was rescinded by Committee on Proprietary Medicinal Products (CPMP) in October 2001. Copyright © 2003 John Wiley & Sons, Ltd.

KEY WORDS — spontaneous reporting; proportional reporting ratios; prescription event monitoring; drug alert

BACKGROUND

Spontaneous reporting is an invaluable and proven way to identify safety signals, despite recognised and well-documented limitations. Most countries have set up such a system, among the best known of which one can cite the British Yellow Card Scheme. To improve the capacity of spontaneous reporting systems to detect signals, beyond the examination of the individual case reports, various frequency or probability-based methods have been devised. The statistical identification of abnormal or unusual reporting patterns that could indicate increased drug risk relies on a number of different approaches, which all give

* Correspondence to: N. Moore, Département de Pharmacologie, Université Victor Segalen-Bordeaux 2, BP36, 33076 Bordeaux, France. E-mail: nicholas.moore@pharmaco.u-bordeaux2.fr

Received 26 July 2002
Revised 11 April 2002
Accepted 5 December 2002

The report:	includes reaction of interest	includes other reactions	Total number
mentions drug of interest	a	b	a+b
does not mention drug of interest	c	d	c+d
PRR	**a/(a+b) / c/(c+d)**		

Figure 1. The 2 × 2 contingency table to calculate the proportional reporting ratio (PRR)

the same results when the number of reports exceeds four.[1] These approaches include Bayesian exploration, neural networks information content and more simply the reporting rate ratios, whether the computation is based on the relative risk (the Medicines Control Agency (MCA)'s proportional reporting ratio (PRR[2]) or the odds ratio (the French case–non-case approach[3]). These are all essentially based on the disproportionality of the reporting of a given event with a specific drug or group of drugs compared to other events and other drugs (Figure 1). The PRR depends both on the occurrence and on the reporting of the events with an interaction that may be more complex than is readily apparent: events that occur may be reported or not and non-events may also be reported as adverse drug reactions. This implies that an alert that is based on the PRR is an alert concerning the relative reporting of events and not their occurrence. In the case of sertindole, such an alert led to the suspension of the drug.

Sertindole is an atypical anti-psychotic that was first marketed in the UK in early 1996. Preclinical data[4,5] and premarketing clinical trials[6,7] had shown the drug's capacity to prolong the QT interval, but without apparently increasing the risk of cardiac death and authorities did not require any strong warning or electrocardiographic (ECG) surveillance upon first licensing. Upon extension of the drug license to other European markets in 1997, authorities asked for a change in the Summary of Product Characteristics (SPC) that would include ECG surveillance prior to and during the treatment with sertindole. A 'Dear Doctor' letter was circulated in the UK to inform doctors about the ECG surveillance. A drug alert regarding sertindole originated subsequently from the UK MCA's database of spontaneous reports, Adverse Drug Reaction Online Information Tracking (ADROIT), in early 1998. The proportion of reports of sudden or unexpected deaths to total reports was about ten times higher for sertindole (7.5%) than for the other atypical anti-psychotics olanzapine (0.8%) and risperidone (0.8%). The signal remained if other causes of death or the total number of prescriptions at the time of the alert were used as denominator (Table 1). This alert and early interim data from an ongoing study[8] led to the worldwide suspension of sertindole in November 1998, pending further evaluation and confirmation of the signal.

Experimental data were not indicative of a severely increased risk of arrhythmia[9] and re-analysis of the data from premarketing clinical trials did not find any indication of excess cardiovascular risk related to arrhythmia, compared with similar trials for the comparators olanzapine and risperidone.[6] Inspection

Table 1. Data giving rise to the sertindole alert in the ADROIT spontaneous reporting database (1998)

	Sertindole	Olanzapine	Risperidone
Reports			
Sudden unexplained death (SUD), *n*	4	2	3
Fatal cardiac arrythmia (FCA), *n*	1	0	1
Non-fatal cardiac arrhythmia (NFCA), *n*	7	10	26
Total number of reports	67	234	492
SUD + FCA (% of total reports)	7.5	0.85	0.81
SUD + FCA + NFCA (% of total reports)	17.9	5.1	6.1
Prescriptions			
Number of prescriptions issued in the UK	12 400	91 900	486 000
SUD + FCA per 1000 prescriptions	0.32	0.02	0.01
All reports per 1000 prescriptions	5.4	2.5	1.01

of individual case reports found multiple possible causes for most of the reported deaths. Because there was no clear immediate confirmation of the excess risk and there were indications of possible bias, we decided to search for further information from other sources, to confirm or refute this alert.

METHODS

In order to study the sertindole signal, we obtained information relating to spontaneous reports, safety studies and utilisation for four atypical anti-psychotics.

Spontaneous reports

Drug analysis printouts (DAPs) were obtained from the MCA, from 1995 to November 1998, date of sertindole's suspension, for sertindole, risperidone, olanzapine and quetiapine, the four atypical anti-psychotics other than clozapine that were marketed during that period. The DAPs included all reports to the MCA, either directly from health professionals or through the holders of the marketing authorisations (MAH). All reports were classified according to ADROIT's Medical Dictionary for Drug Regulatory Authorities (Meddra) classification system.

Individual case reports of deaths related to sertindole were obtained from the manufacturer of sertindole and analysed for causality.[10] It was not possible to obtain these data from the other MAH holders.

Drug utilisation

Drug sales data of the four atypical anti-psychotics of interest in the UK were obtained from IMS (UK) from the date of market introduction to the year 2000. The sales data were translated in number of days of treatment sold assuming intake of one Defined Daily Dose (DDD)[11] per day and subsequently expressed in person-years exposed to treatment (PYE).

Post-marketing studies

Prescription event monitoring studies (PEM). The PEM studies for sertindole, risperidone and olanzapine were obtained.[12–14] The one concerning risperidone had been available in 1998, the others later in 1999–2000. No such study was available concerning quetiapine. Data extracted from these publications comprised exposure and the total number of deaths for each drug. The methodology of PEM studies has been described previously.[15,16] In brief, the first 10 000–15 000 prescriptions of study drugs are obtained from the UK's Prescription Pricing Authority. Each prescriber is sent a form on which the medical events of the first 6 months or the first year after the initial prescription can be reported. Participation is voluntary and the return rate is typically around 60%. In case of non-response, the prescriber may be contacted. This was done for the PEM study on sertindole,[13] whereas limited non-response follow-up was completed for olanzapine and none for risperidone. Due to these differences in data collection, cause-specific death rates could not be compared between sertindole, olanzapine and risperidone.

European Sertindole Exposure Study (ESES).[17] A European post-marketing surveillance study was initiated by the marketing license holder of sertindole during 1998–1999. All psychiatrists who participated in trials or requested drug samples and other prescribers who were identified through the sales network were contacted and asked to identify those of their patients who had been treated with sertindole and complete a case report form for all such patients. The case report form included information on the dates of treatment onset, change and cessation, the reasons for start and cessation and the last known vital status (date and cause of death or date of last consultation).

Analysis

Several measures were used to study the PRR signal:

- PRRs for sertindole versus the other atypical neuroleptics were calculated from the ADROIT data both in 1998 (the alert) and in April 2000, as the ratios of the number of case reports of a given event (such as sudden or arrhythmic deaths) to all reports concerning sertindole, to the same ratio for comparators (Figure 1).
- Report rates were computed as the ratio of the number of reports to the amount of drug utilisation, expressed as thousand prescriptions, as sales in number of patient-years of drug sold or as patient-time exposure in studies.
- Finally the reporting rate was computed as the percentage of the number of cases reported to the number of cases that actually occurred in the same population.

To see whether time since first marketing and total cumulative population exposure may affect the report rates and thereby the PRR if comparators have different marketing lives or patterns, we calculated the instantaneous and cumulative report rates (number

of cases reported up to a certain date divided by sales in patient-years to that date). The latter approach was chosen since regulatory decisions usually rest upon the cumulative numbers of cases at a given time-point. To explore the effect of amount of exposure on the pattern of the cumulative report rate, report rates were also plotted against the simultaneous cumulative amount of exposure.

Since spontaneous report databases do not contain all cases that occur and the validity of the PRR rests on equal report rates for the different drugs, we tried to calculate the under-reporting rates for the different drugs. To get an idea of the amount of under-reporting to the ADROIT database, we compared the death rates of the PEM studies with reported death rates calculated on the basis of spontaneous reports and patient-years of drugs sold.

Because of the small number of deaths in the sertindole PEM study and because the manufacturer of sertindole had descriptions of the cases included in the MCA database, it was possible to reconcile the cases occurring in the PEM study, and those reported, without having to breach patient confidentiality. This allowed for a direct calculation of the percentage of cases that were actually reported to MCA (reporting rate). A similar approach was not possible for the other atypical anti-psychotics. The percentage of reporting estimate for olanzapine and risperidone was therefore completed in a best or worst-case scenario by dividing the cases that ever occurred during the lifetime of the drugs in the UK by the number of deaths reported in the respective PEM studies.

In addition, the reporting of cases with sertindole to MCA and to PEM over the same period and geographical area allowed us to use a capture–recapture method to estimate the total number of cases that occurred, using the standard formula:[18]

$$N = \frac{(n_{PEM} \times n_{MCA})}{n_{PEM\ and\ MCA}},$$

where N is estimated total number of cases,
n_{PEM} = number of cases reported to PEM,
n_{MCA} = number of cases reported to MCA and
$n_{\mathrm{PEM\ and\ MCA}}$ = number of cases reported to both PEM and MCA.

Confidence intervals were computed using the Poisson distribution.

The ESES Study was used to identify potential differential reporting by cause of death: all deaths that occurred in these patients were identified and compared to those that had been reported to authorities or to the MAH, overall and by cause.

RESULTS

Spontaneous reporting: PRRs from the MCA database ADROIT in 1998 and 2000

The initial alert regarding sertindole was raised on the basis of the data that are provided in Table 1. The PRR regarding sudden death and fatal arrhythmia was almost tenfold higher for sertindole than for olanzapine or risperidone: these causes represented 7.5% of all sertindole related spontaneous reports versus 0.8% of olanzapine and risperidone reports. The difference between sertindole and the other anti-pyschotics was also large if the report rate was expressed in terms of prescriptions, with 0.32 reports of sudden death or fatal arrhythmia per thousand prescriptions with sertindole, compared to 0.02 for olanzapine and 0.01 with risperidone. It should be noted that the overall report rate was higher for sertindole (5.4 reports/1000 prescriptions) than for olanzapine (2.5/1000 prescriptions) or risperidone (1.0/1000 prescriptions) (Table 1).

When the data were updated in April 2000 (Table 2), one of the four initial reports of sudden death with sertindole had been reclassified as a non-cardiac cause. The PRR of sudden unexplained death and fatal arrhythmia had diminished from almost ten to just above three, based on revised relative reporting rates of 3.8% 1.2% and 0.6% for sertindole, olanzapine and risperidone, respectively.

Spontaneous reporting: patterns of reporting over time and cumulative use

The report rates for sertindole in the UK clearly reflect a series of events, including the initial 'Weber effect',[19] a sharp increase in reports after the 'Dear Doctor' letter and smaller increases in report rates upon adverse publicity concerning the suspension of sertindole (Figure 2).

Figure 3 shows the cumulative report rate for all fatal reports and all four atypical anti-psychotics (1996–1998). Fatal report rates seem higher with sertindole and quetiapine than with olanzapine and risperidone, but clearly depend upon the time of analysis. For risperidone, which was marketed several years prior to sertindole, the report rate seems consistent with the tail end of the Weber curve. Olanzapine, which was marketed at the same time as sertindole but had a much larger market share, seems to have much lower report rates, even though a small Weber effect is visible. Plots of the cumulative report rates against the amount of exposure showed a sharp decline of reporting rates with increasing cumulative exposure and all

Table 2. Spontaneous reports in the UK (ADROIT data) until April 2000 and reporting rates

	Sertindole	Olanzapine	Risperidone
Reports			
All-cause deaths	9	27	23
Cardiovascular deaths	5	18	9
Sudden unexplained death (SUD)	3	8	2
Fatal cardiac arrhythmia (FCA)	1	2	2
Non-fatal cardiac arrhythmia (NFCA) (excl. QT prolongation)	5	22	35
QT prolongation*	14	5	2
Total reports	105	809	715
SUD + FCA (as % of total reports)	3.81	1.24	0.56
SUD + FCA + NFCA (as % of total reports)	8.57	3.96	5.45
Total exposure (× 100 PYE)	17.69	919.71	922.67
All-cause reported fatality rate per 100 PYE	0.509	0.029	0.025

*ECG monitoring mandatory only for sertindole.
PYE: person-years exposed from sales data.

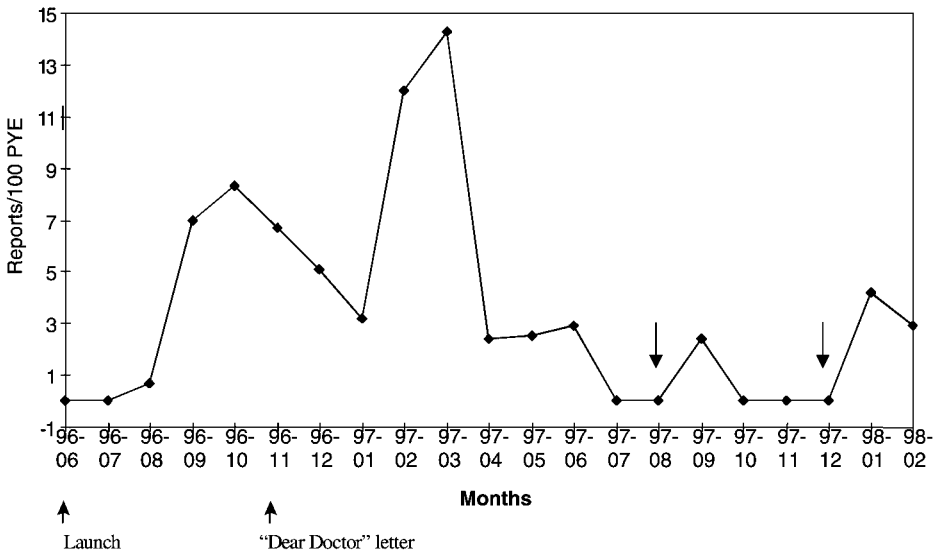

Figure 2. Monthly reporting rates per 100 PYE for sertindole in the UK (arrows indicate adverse publicity)

four drugs seemed to follow the same curve for all case reports and for fatal case reports, so that for a given market exposure there does not seem to be any clear difference in report rate between the drugs (Figures 4 and 5) for all or fatal events.

Post-marketing studies: PEM and assessment of reporting rates

The results of the PEM studies concerning sertindole, olanzapine and risperidone are summarised in Table 3. Patient exposure and study size differed considerably between studies, with a lower amount of exposure time for sertindole. The overall death rates were similar for the three drugs. The point estimate of the all-cause mortality rate ratio between sertindole and the two other drugs combined was 0.6, with a 90% confidence interval of 0.31–1.1 (which excludes with less than 5% chances of being wrong a ratio above 1.1). Since the case ascertainment was not the same in the different studies, it was not possible to study cause-specific rates of death.

Comparison of the PEM mortality rate and the mortality rate based on spontaneous reporting in the UK showed that apparently about 0.9 %, 0.5% and 22% of deaths were reported to ADROIT for olanzapine,

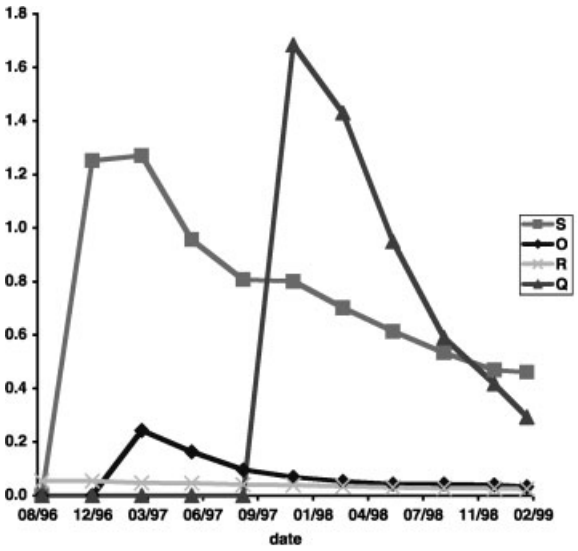

Figure 3. Cumulated report rates for fatal reaction reports, per 100 person-years treatment sold, for Sertindole (S), Olanzapine (O), Risperidone (R), and Quetiapine (Q) over time

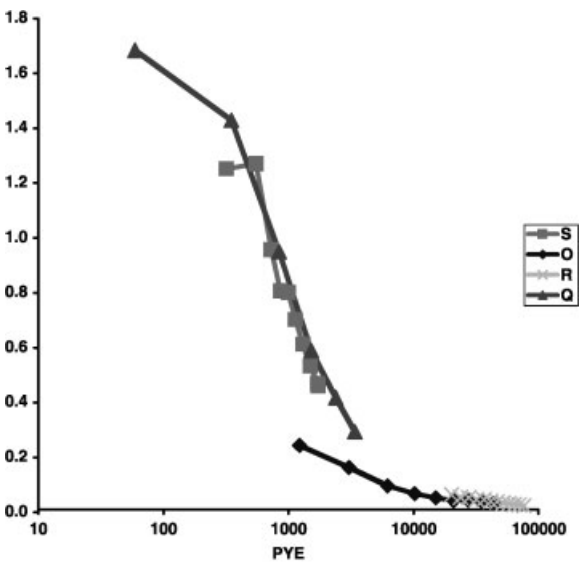

Figure 5. Evolution of cumulated number of reports of deaths per 100 PYE (report rate) as a function of total PYE sold, for sertindole (S), olanzapine (O), risperidone (R) and quetiapine (Q)

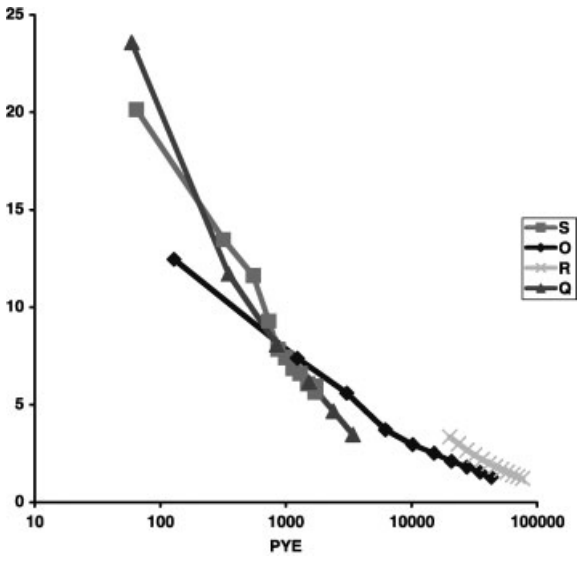

Figure 4. Evolution of cumulated number of reports of any reaction per 100 PYE (report rates), as a function of total PYE sold, for sertindole (S), olanzapine (O), risperidone (R) and quetiapine (Q)

risperidone and sertindole respectively (Table 3). Direct case comparison of deaths showed that two of the seven cases in the sertindole PEM had also been reported to MCA (29%). During the time of the sertindole PEM study, five fatal cases from the PEM catchment area were reported to the MCA, two of which were also identified in the PEM study, as stated. Based on the capture–recapture method,[18] the total number of deaths that occurred in the catchment area can be estimated at 17.5 cases (95% Poisson confidence interval 9.9–27.2). Five cases had been reported to the MCA, resulting in an estimated reporting rate of 28.5% (95%CI: 18–50%). It is not known how many of the fatal cases reported in the olanzapine and risperidone PEM studies were also reported to the MCA, so that the same computation is not possible for these drugs. However, in an extreme scenario, if all the cases ever reported during the marketing life of the drugs in the UK had occurred during the PEM, the reporting rates would only have been 5.4% for olanzapine and 8.1% for risperidone.

The ESES study

A total of 8608 patients were included in the ESES study, cumulating 3819 patient-years of exposure to sertindole. Thirty-five patients had died during sertindole treatment, resulting in a death rate of 0.9 per 100 patient-years exposure (95%CI: 0.64–1.35). Overall, 46% of these deaths had been previously reported to the company or to the health authorities. This reporting rate was 73% for cardiac deaths, but only 25% for suicides (Table 4).

Table 3. Prescription Event Monitoring (PEM) studies and comparison with ADROIT data

	Sertindole	Olanzapine	Risperidone
PEM			
Number of patients included	462	8858	7684
PYE†	299	5805	4449
Number of deaths	7	194	221
All-cause observed fatalities per 100 PYE	2.34	3.34	4.97
(95%CI)	(0.94–4.83)	(2.87–3.83)	(4.27–5.60)
ADROIT (from Table 2)			
All-cause reported fatality rate per 100 PYE	0.509	0.029	0.025
Comparison ADROIT/PEM			
Reporting rate (%)*	21.7	0.87	0.50

*Reporting rate calculated as the ratio of the ADROIT derived all-cause reported fatality rate and the PEM derived all-cause fatality rate.
†PYE: person-years exposed.

Table 4. Reporting of deaths in the ESES study

Cause of death	All deaths	Cardiac	Not ascertained	Suicide	Other
Number of deaths in ESES study	35	11	8	8	8
Deaths reported spontaneously	16	8	3	2	3
Reporting rate* (%)	46	73	38	25	38

*Reporting rate calculated by dividing the number of spontaneously reported deaths by the number of deaths reported in the ESES study.

DISCUSSION

The sertindole signal generated in the ADROIT spontaneous reporting database concerned an increased rate of *reporting* of sudden death related to a drug known to prolong the QT interval. This resulted in the drug being suspended from the market. The individual cases of sudden death themselves were unremarkable, with many alternate or competing explanations for the deaths: e.g. sudden death in an overweight, diabetic, hypertensive heavy smoker with known coronary heart disease, who dies suddenly while walking uphill may not be entirely drug-related. In none of the cases was there any recorded evidence of arrhythmia, so that in effect, the suspension was based mainly on the PRR finding. However, it would appear in retrospect that this PRR signal might well have been generated by differential reporting of death in general and cardiovascular death in particular.

Sudden death is a feature of schizophrenia, first reported before neuroleptics were ever used.[20] It has been associated with most, if not all, neuroleptics at therapeutic or toxic doses.[21] Many neuroleptic drugs, including sertindole, increase the QT interval,[4,22] probably by inhibition of the HERG cardiac potassium channel.[23] The ADROIT database contains reports of QT prolongation, sudden death, ventricular arrhythmia or *torsade de pointes* for most neuroleptics including olanzapine, risperidone and quetiapine. QT prolongation is an asymptomatic pro-arrhythmic risk factor. Arrhythmias can also be asymptomatic. Both will be detected only if an ECG is recorded. ECG monitoring at that time was mandatory only for sertindole, not for other neuroleptics, so that different report rates of QT prolongation or asymptomatic arrhythmia must be expected and cannot be interpreted as indicating different risks. In addition, the 'Dear Doctor' letter emphasised the need for close ECG monitoring during the use of sertindole, but not during use of other neuroleptics, compounding any differential identification, attribution and reporting of cardiovascular (and possibly other) adverse events. This reporting bias is demonstrated by the clear temporal relationship between the 'Dear Doctor' letter and a surge in the report rates, the higher report rate of deaths with sertindole than with olanzapine or risperidone compared to similar PEM death rates and the greater reporting of cardiac deaths than other deaths in the ESES study. Despite limitations of the PEM study, the death rates identified correspond well with those reported elsewhere for schizophrenia.[24,25] A re-analysis of the premarketing clinical trials of sertindole, olanzapine and risperidone showed similar overall death rates of about 1.9 per hundred patient-years of exposure.[6,7]

Death rates in schizophrenic patients are estimated in the UK to be 2–5 per hundred patient-years.[25] The PEM study showed death rates between drugs that were similar, with a slightly higher all-cause mortality rate for risperidone. The mortality rate ratio in the PEM studies suggests that the all-cause death rate with sertindole is no higher than 1.1 times that of olanzapine and risperidone combined (upper limit of the 90% confidence interval of the rate ratio), despite the small size of the sertindole PEM study.

These *post hoc* analyses do not exclude that there may or may not be a problem with sertindole. However, the data clearly suggest that the initial increased PRRs might be explained by differential reporting. Reanalysis of all data showed no discernible difference in death rates and certainly not the tenfold difference suggested by the PRR. Considering the rates of death in these patients, the truth may be obtained through a large-scale prospective randomised pragmatic real-life mortality study, which is actually underway, now that the drug has been re-admitted to the market.

The main frailty of an alert based on spontaneous reporting is the data on which it relies and its inherent biases. Biases can affect each of the four boxes of the 2×2 PRR contingency table in different ways. Some of the biases relate to event occurrence, some to event identification and reporting, and finally some to proportional reporting rate ratio analyses specifically.[3]

The channelling of drugs to lower or higher risk patients may alter the occurrence rate of events. These occurrence rates may be further modified by avoidance of risk factors associated with the event. This will introduce bias unless all the cells of the 2×2 table for calculation of the PRR are affected equally. The PRR can also be skewed if the drug of interest causes lower rates of occurrence of other, non-serious reactions because of either its properties or the choice of treated population. This may be the case for higher relative rates of hepatic reactions in users of COX-2 inhibitors, because of lower rates of GI events or higher relative rates of cardiac events for anti-psychotics that do not induce extra-pyramidal syndromes or weight increases. Hence a drug with a good tolerability profile may trigger a signal for the same number of serious events as another drug with a poorer general tolerability profile.

In an ideal world, all adverse drug reactions will be reported. This is not the case and it is estimated that even the reporting rate (proportion of the reactions that actually occur that are reported) for serious adverse drug reactions is below 10%.[26–28] The second best situation would be that the same proportion of all serious ADRs is reported. This is not necessarily true either, for example, unexpected, unlabelled serious reactions have a higher reporting rate than expected.[27,28] As a final line of retreat, one could hope that the under-reporting will affect different drugs in the same way. Again, as we saw, this may not be true either. Differential reporting may affect the PRR in unpredictable ways.

For an adverse reaction to be reported, it will need to be identified as an adverse reaction, then attributed to a drug (or drugs) and finally reported. Adverse event identification and reporting rates may be higher if there have been warnings about a drug ('notoriety bias'), or specific surveillance recommendations. Notority bias can be extremely strong and even override common sense.[29] The same event may be recognised as an adverse reaction and reported or shrugged off as being a fact of life and not reported, especially when causality is difficult to establish such as for sudden death. Sudden death occurring in a patient with coronary heart disease may not be reported if the patient was a known case of arrhythmia and was treated for it or, on the other hand, will be reported if the patient was treated with an H1 anti-histamine or a neuroleptic suspect of causing *torsade de pointes* or sudden death. Cases have been seen of reports of sudden death attributed to drug A that was stopped several weeks before, while drug B, recently introduced and taken at the time of death is not considered, because (*sic!*) it is well-known that drug A causes sudden death. Specific surveillance recommendations may lead to higher rates of identification and reporting. A prime example is that given above for sertindole and ECG monitoring resulting in increased identification of arrhythmias. The warning becomes self-fulfilling if there is a significant background rate of events in the treated population. More active monitoring of its drug by a pharmaceutical company may even further distort reporting.

The possibility of correcting this reporting bias may vary according to the possibility of causality assessment. If the event has clear causality criteria, there may be little doubt that the event is really drug related,[30,31] for instance, events that recede after drug withdrawal, have a positive re-challenge or signs indicative of a specific drug action or when other non-drug causes can be eliminated. In addition, it is often clear from the case reports which drug is the most probable cause. When the event is unexplained sudden death, there is by definition no de-challenge or re-challenge, and there is often no way to eliminate other causes, especially pro-arrhythmic abnormalities which leave no post-mortem fingerprints. The concomitant use of other medication, for example for suicidal intent may

not be easy to demonstrate. The presence of clogged or altered coronary arteries and the known use of other pro-arrhythmic medication may lead to alternate conclusion of explained death (drug not involved) or that the role of the suspect drug cannot be excluded. This underlines the need for clear consensus criteria on the attributability of events as reactions. These exist for hepatic, skin and haematological reactions, but not for sudden death.

Differential reporting of non-serious events can affect any calculated ratios in the same way as differential occurrence. If there is clear knowledge and labelling of these non-serious events, there may be less reporting than if the event is not expected to happen with the drug: e.g. for COX-2 inhibitors, one could expect relative over-reporting of non-specific gastrointestinal (GI) complaints, since those are not supposed to happen with these 'safe' drugs. Channelling of these drugs to higher-risk patients will compound this reporting bias.

The choice of the comparator drug(s) is of utmost importance to the appropriateness of the PRR: the use of a given drug may select populations at higher risk of certain adverse reactions. For instance, ACE inhibitors are the treatment of choice of hypertension in diabetics. If one compares the occurrence of hypoglycaemia associated with the use of ACE inhibitors to that of the background population of other reports in a spontaneous reporting database, there will be a clearly increased PRR, that disappears when the comparator population is stratified according to concomitant use of anti-diabetic agents, which themselves cause hypoglycaemia.[3] On the other hand, the association of hypoglycaemia with cibenzoline persisted despite this stratification. However, using comparators within the same therapeutic class may not always be a safeguard, if there are indications of channelling of one drug to higher-risk patients, as could be the case for GI bleeding and COX-2 inhibitors. This may be perfectly appropriate from a therapeutic point of view and in fact be good medical practice, but it may increase the apparent rate of events, if this channelling is not taken into account.[32–34]

As it is used, the PRR is tested at a given point in time when the alert occurs. Reporting of adverse reactions, however, varies over time. It is usually at maximum just after market launch and it subsequently tapers off (the Weber effect). Therefore potential comparators in the same therapeutic class may be at different stages of the Weber curve. There is a possibility of a differential Weber effect for different reactions (e.g. serious vs non-serious). It may be that changes over time in reporting rate ratios may be as important as the actual absolute value. These changes may be studied on the actual risk over given time periods or as the cumulative PRR. A dynamic PRR may well confirm or refute the results of a static PRR.

Finally, an administrative bias: European rules and regulations state that all serious reactions, (as legally defined) must be reported to the authorities within 15 days of receipt by the manufacturer and *vice versa*. On the other hand, non-serious reports will be included in the so called periodic safety update reports, usually as consolidated reports, with very little information on individual cases. Usually, the PRRR or its congeners is computed on reporting databases in the regulatory authorities or similar databases, such as the French Pharmacovigilance database, the ADROIT system in the UK, the FDA in the US or the WHO UMC system in Uppsala. Since alerts are usually driven by serious reports, inclusion of serious manufacturer reports in the database and in the computation of the PRRR will increase the numerator without affecting the denominator, the vast bulk of which is made of non-serious reports. Since the reporting of the manufacturers depends on the intensity of their monitoring activities, a bias could be introduced which favours those manufacturers that are least active in monitoring of their drugs. To avoid this potential bias in the PRR calculation, one should only include the reports that come through the same channel, i.e. in this case, usual direct reports from physicians.

CONCLUSIONS

Spontaneous reporting is an alert-generating system. The PRR or any other test of disproportionality can only be as good as the data it relies on. It is only a measure of the disproportionality of *reporting* of adverse reactions and not of their actual *occurrence*. Although it is valuable for signal identification, it cannot be considered a hypothesis-validating tool or at least should probably not be used as such. At the very least, biases that could affect the PRR should be carefully sought for and accounted for. The PRR should be used with particular care when previous regulatory (change in SPC) or publicity activity has taken place or when drugs within a similar therapeutic class have different monitoring requirements and marketing life cycles unless one wishes to have self-fulfilling predictions.

Ideally, the PRR should be used to hypothesise on the presence of newly identified drug-reaction associations in a stable system, using only similarly obtained data and followed over time. In any event,

the PRR will only give information on proportional reporting of events, never on proportional occurrence of events. Disproportionality in occurrence rates can only be tested with well-designed analytic studies, and such should be performed before taking drastic regulatory actions in the absence of an imminent major health hazard.

The suspension of sertindole in November 1998 was motivated by an increased PRR and by the existence of an initially slightly higher event rate in the sertindole than in the comparator arm of the EPOS study. Sertindole may have prolonged the QTc more than some of the other neuroleptics, even though there was no indication from preclinical or clinical trial data of any increased risk of arrhythmia. We could not substantiate the increased risk of fatal arrhythmia or sudden death with sertindole post-marketing and instead found evidence of differential reporting that could explain the skewed PRR. The EPOS study was suspended prematurely because of the drug's suspension. By that time, over 1000 patients had been included in each study arm and there was not a single cardiac death in either arm. The overall death rates were similar in both study arms (1.45 per 100 PYE vs 1.50 per 100 PYE), lower than in premarketing trials and at no time was any imbalance between the arms significant. We considered that the initial signal was not confirmed. The CPMP concurred and recommended that the suspension of sertindole be lifted with appropriate surveillance, on 17 October 2001, almost 3 years after it was suspended.

CONFLICT OF INTEREST DISCLOSURE

Authors of this article (NM, GH, MS, RM) acted in a consultant capacity for the Marketing Authorization Holder of sertindole and appeared before the Committee on Proprietary Medicinal Products (CPMP) and a CPMP Expert Committee convened to consider the issue discussed in this article.

All reviews and decisions related to this manuscript were managed exclusively by the US office of the Journal.

KEY POINT

- Automated measures of spontaneous reporting disproportionality need confirmation from other sources before drastic decisions are made, in the absence of a clear and immediate danger to public health.

REFERENCES

1. van Puijenbroek EP, Bate A, Leufkens HG, Lindquist M, Orre R, Egberts AC. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiol Drug Safe* 2002; **11**(1): 3–10.
2. Evans SJ, Waller PC, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiol Drug Safe* 2001; **10**(6): 483–486.
3. Moore N, Kreft-Jais C, Haramburu F, *et al.* Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol* 1997; **44**(5): 513–518.
4. Drici MD, Wang WX, Liu XK, Woosley RL, Flockhart DA. Prolongation of QT interval in isolated feline hearts by antipsychotic drugs. *J Clin Psychopharmacol* 1998; **18**(6): 477–481.
5. Rampe D, Murawsky MK, Grau J, Lewis EW. The antipsychotic agent sertindole is a high affinity antagonist of the human cardiac potassium channel HERG. *J Pharmacol Exp Ther* 1998; **286**(2): 788–793.
6. Moore N, Lagnaoui R, Toumi M, Bégaud B. Suicide and sudden death during treatment with atypical neuroleptics: a comparison of sertindole, olanzapine and risperidone In VII International Congress on Schizophrenia Research *April 17–21* 1999. Santa Fe, 1999.
7. Moore N, Lagnaoui R, Bégaud B. Assessing the risk of cardiac death with sertindole: data from clinical trials; comparison with risperidone and olanzapine. In *15 International Conference on Pharmacoepidemiology 26–29 August 1999*. Boston, 1999.
8. Wehnert A. The European post-marketing observational serdolect® (EPOS) project: increasing our understanding of schizophrenia therapy. *Int Clin Psychopharmacol* 1998; **13**(Suppl. 3): 27–30.
9. Eckardt L, Breithardt G, Haverkamp W. Electrophysiologic characterization of the antipsychotic drug sertindole in a rabbit heart model of torsade de pointes: low torsadogenic potential despite QT prolongation. *J Pharmacol Exp Ther* 2002; **300**(1): 64–71.
10. Begaud B, Evreux JC, Jouglard J, Lagier G. Imputation of the unexpected or toxic effects of drugs. Actualization of the method used in France. *Therapie* 1985; **40**(2): 111–118.
11. Wertheimer AI. The defined daily dose system (DDD) for drug utilization review. *Hosp Pharm* 1986; **21**(3): 233–234, 239–241, 258.
12. Mackay FJ, Wilton LV, Pearce GL, Freemantle SN, Mann RD. The safety of risperidone: a post-marketing study on 7684 patients. *Human Psychopharmacol Clin Exp* 1998; **13**: 413–418.
13. Wilton LV, Heeley EL, Pickering RM, Shakir SA. Comparative study of mortality rates and cardiac dysrhythmias in post-marketing surveillance studies of sertindole and two other atypical antipsychotic drugs, risperidone and olanzapine. *J Psychopharmacol* 2001; **15**(2): 120–126.
14. Biswas PN, Wilton LV, Pearcel GL, Freemantle S, Shakir SA. The pharmacovigilance of olanzapine: results of a post-marketing surveillance study on 8858 patients in England. *J Psychopharmacol* 2001; **15**(4): 265–271.
15. Inman WH. Postmarketing surveillance of adverse drug reactions in general practice: in search for new methods. *Br Med J (Clin Res Ed)* 1981; **282**(6270): 1131–1132.
16. Mackay FJ. Post-marketing studies: the work of the Drug Safety Research Unit. *Drug Safe* 1998; **19**(5): 343–353.

17. Peuskens J, Moore N, Azorin JM, Toumi M. Sertindole safety and exposure: a retrospective study on 8608 patients in Europe. In *18 ICPE 19–21 August 2002*. Edinburgh, 2002.
18. Begaud B. *Dictionary of Pharmacoepidemiology.* Chichester: Wiley, 2000.
19. Wallenstein EJ, Fife D. Temporal patterns of NSAID spontaneous adverse event reports: the Weber effect revisited. *Drug Safe* 2001; **24**(3): 233–237.
20. Peele R, Von Loetzen IS. Phenothiazine deaths: a critical review. *Am J Psychiatry* 1973; **130**(3): 306–309.
21. Ray WA, Meredith S, Thapa PB, *et al.* Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry* 2001; **58**(12): 1161–1167.
22. Adamantidis MM, Kerram P, Dupuis BA. *In vitro* electrophysiological detection of iatrogenic arrhythmogenicity. *Fundam Clin Pharmacol* 1994; **8**(5): 391–407.
23. Welch R, Chue P. Antipsychotic agents and QT changes. *J Psychiatry Neurosci* 2000; **25**(2): 154–160.
24. Montout C, Casadebaig F, Lagnaoui R, *et al*. Neuroleptics and mortality in schizophrenia: prospective analysis of deaths in a French cohort of schizophrenic patients. *Schizophr Res* 2002; **57**(2–3): 147.
25. Baxter DN. The mortality experience of individuals on the Salford Psychiatric Case Register. I. All-cause mortality. *Br J Psychiatry* 1996; **168**(6): 772–729.
26. Begaud B, Martin K, Haramburu F, Moore N. Rates of spontaneous reporting of adverse drug reactions in France. *JAMA* 2002; **288**(13): 1588.
27. Martin RM, Kapoor KV, Wilton LV, Mann RD. Underreporting of suspected adverse drug reactions to newly marketed ('black triangle') drugs in general practice: observational study. *Br Med J* 1998; **317**(7151): 119–120.
28. Alvarez-Requejo A, Carvajal A, Begaud B, *et al.* Under-reporting of adverse drug reactions. Estimate based on a spontaneous reporting scheme and a sentinel system. *Eur J Clin Pharmacol* 1998; **54**(6): 483–488.
29. Lagier G, Vincens M, Castot A. Imputability in drug monitoring. Principles of the balanced drug reaction assessment method and principal errors to avoid. *Therapie* 1983; **38**(3): 303–318.
30. Danan G. Causality assessment of drug-induced liver injury. Hepatology Working Group. *J Hepatol* 1988; **7**(1): 132–136.
31. Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993; **46**(11): 1323–1330.
32. Van Ganse E. Use of databases in pharmacovigilance: two examples. *Therapie* 1995; **50**(5): 409–412.
33. Spitzer WO, Suissa S, Ernst P, *et al*. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; **326**(8): 501–506.
34. Blais L, Ernst P, Suissa S. Confounding by indication and channeling over time: the risks of beta 2-agonists. *Am J Epidemiol* 1996; **144**(12): 1161–1169.

